THE EFFECT OF A 12 MONTH INTRADIALYTIC EXERCISE INTERVENTION ON FUNCTION, QUALITY OF LIFE, NUTRITIONAL STATUS AND CLINICAL STATUS

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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For C.C.S my NSEW and in memory of M.S & W.M.B.S

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ABSTRACT

Haemodialysis (HD) patients are reported to have low levels of physical function, poor quality of life, protein energy wasting and inflammation, which negatively impact on morbidity and mortality. Exercise has previously been used as an intervention in HD patients; however the majority of previous studies have been of short duration and utilised moderate or high intensities requiring individual supervision of each exercise session. These studies recruited young patients with low levels of comorbidity and primarily focused on changes in VO_2max/peak. This limits the ability to generalise findings to the wider prevalent HD population. The aims of the present study were therefore to determine whether a low to moderate intensity intradialytic exercise intervention with broad applicability, could over a 12 month period improve functional status and in turn quality of life, nutritional status and clinical status in a prevalent HD population in Scotland.

Patients were recruited from NHS Fife, to a non-randomised controlled study and followed a progressive intradialytic aerobic exercise programme. One exercise session was conducted with individual supervision and two sessions with general supervision from dialysis staff. Outcome measures included measures of function (sit to stand, timed up and go, and handgrip), quality of life (SF36v2), nutritional status (anthropometric measurements, dual frequency bioelectrical impedance analysis, dietary intake and appetite) and clinical status (dialysis adequacy, biochemistry, high sensitivity C-reactive protein, blood pressure, medications). Measurements were taken at 6 time points: -1, 0, 3, 6, 9 and 12 months.

25 patients (mean age 56 $\pm$ 11.4 years) volunteered for the intervention and 13 patients (mean age 60.8 $\pm$ 14.6 years) volunteered as controls. At baseline groups demonstrated functional impairment, poor quality of life, and low fat free mass and had evidence of low grade inflammation. 25 patients completed 3 months of the exercise intervention, 20 completed 6 months, 16 completed 9 months and 13 patients completed 12 months. Of the 13 control patients 6 remained at 3 months and 5 at 6 months.

In the exercise group, significant improvements were observed in all measures of function and 6 out of 8 physical and psychosocial quality of life domains. Anthropometric measures of fat free mass increased. Clinical status improved significantly seen as reductions in systolic blood pressure and prescribed erythropoietin stimulating agent doses. These improvements were observed in the intervention group at 3 and 6 months. No improvements were observed in the control group. Improvements in the majority of outcome measures were also seen in the intervention group at 6 and 12 months.

These results suggest that the introduction of a low to moderate intensity intradialytic exercise programme requiring minimal individual supervision is feasible and provides clinically significant improvements in function from 3 months onwards. Such improvements are accompanied by higher quality of life scores and improved aspects of nutritional and clinical status.

Key words: Haemodialysis, intradialytic exercise, function, quality of life, nutritional status, clinical status.

ABBREVIATIONS

6MWT: 6 Minute Walk Test
%: Percentage
ABP: Ambulatory Blood Pressure
ACSM: American College of Sports Medicine
ADAT: Appetite and Diet Assessment Tool
AI: Augmentation Index
Alb: Albumin
BCM: Body Cell Mass
BIA: Bioelectrical Impedance Analysis
BMC: Bone Mineral Content
BMI: Body Mass Index
BNP: Brain Natriuretic Peptide
BP: Bodily Pain
BW: Body weight
CC: Calf Circumference
CSF: Calf Skinfold
CKD: Chronic Kidney Disease
cm: centimetres
CMC: Calf Muscle Circumference
Cr: Creatinine
CRP: C-Reactive protein
CVA: Cerebrovascular Disease
DBP: Diastolic Blood Pressure
DFBIA-ECW: Dual frequency bioelectrical impedance analysis-extracellular water
DFBIA-FM: Dual frequency bioelectrical impedance analysis-fat mass
DFBIA: Dual frequency bioelectrical impedance analysis
DFBIA-FFM: Dual frequency bioelectrical impedance analysis-fat free mass
DFBIA-%FM: Dual frequency bioelectrical impedance analysis-percentage fat mass
DFBIA-ICW: Dual frequency bioelectrical impedance analysis-intracellular water
DFBIA-%FFM: Dual frequency bioelectrical impedance analysis-percentage fat free mass
DFBIA-TBW: Dual frequency bioelectrical impedance analysis-total body water
DXA: Dual energy x-ray absorptiometry
DXA-FM: Dual energy x-ray absorptiometry-fat mass
DXA-FFM: Dual energy x-ray absorptiometry-fat free mass
ECW: Extracellular water
EDTA: European Dialysis and Transplant Association
eKt/v: equilibrated Kt/v
ESA: Erythropoietin stimulating agent
F: Female
FFM: Fat Free Mass
FM: Fat Mass
g: Gram
g/dl: grams per decilitre
GFR: Glomerular Filtration Rate
GH: General Health
Hb: Haemoglobin
Hct: Haematocrit
HD: Haemodialysis

HDL: High Density Lipoprotein
HGD: Handgrip dynamometry
HGS: Handgrip strength
HR_{max}: Maximal heart rate
HsCRP: High sensitivity C-reactive protein
IBW: Ideal body weight
ICC: Intraclass correlation coefficient
ICU: Intensive Care Unit
ICW: Intracellular water
IGF: insulin like growth factor
IL-1: Interleukin-1
IL-6: Interleukin-6
ISAK: International Society for the Advancement of Kinathropometry
IVNA: *in vivo* neutron activation analysis
K^+:Potassium
kcal: Kilocalories
kg: Kilograms
kHz: Kilohertz
LSTM: Lean soft tissue mass
m: metres
M: Male
MAC: Mid arm circumference
MAMC: Mid arm muscle circumference
MCS: Mental component summary
mcg: micrograms
mg: milligrams
MH: Mental health
MI: Myocardial infarction
mIGFBP-3:muscle insulin- like growth factor binding protein 3
ml: millilitres
mm:millimetres
mmHg: millimetres mercury
mmols: millimoles
mmols/l: millimoles per litre
mg/l: milligrams per litre
mRNA: messenger ribonucleic acid
NHS: National Health Service
NHANES: National Health and Nutritional Examination Survey
NSRI: North Staffordshire Royal Infirmary
nPCR: normalised Protein Catabolic Rate
PCR: Protein Catabolic Rate
PCS: Physical Component Summary
PD: Peritoneal dialysis
PEW: Protein energy wasting
PF: Physical functioning
PWV: Pulse wave velocity
QMU: Queen Margaret University
QOL: Quality of Life
RP: Role Physical
RE: Role Emotional
RM ANOVA: Repeated Measures Analysis Of Variance
RPE: Ratings of Perceived Exertion
RRT: Renal Replacement Therapy

SBP: Systolic Blood Pressure
SD: Standard Deviation
SEM: Standard Error of Mean
SF: Social Functioning
SF-36: Short Form 36
SF-36v2: Short Form 36 version 2
SGA: Subjective Global Assessment
SIGN: Scottish Intercollegiate Guideline Network
SS: Sit to Stand
SSR: Scottish Renal Registry
TBW: Total Body Water
TEM: Technical error of measurement
TNF-α: Tumour Necrosis Factor -alpha
TSF: Tricep Skinfold
TUG: Timed Up and Go
UK: United Kingdom
UKM: Urea Kinetic Modelling
µmols: micromoles
URR: Urea Reduction Ratio
USA: United States of America
VAS: Visual Analogue Score
VT: Vitality
VO_2max: Maximal Oxygen Uptake
VO_2peak: Peak Oxygen Uptake
WHO: World Health Organisation
WTE: Whole Time Equivalent

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DECLARATION

I declare that the work contained within this thesis is original. I have solely been responsible for the organisation and day to day running of the study contained herein, as well as all of the aspects of data collection and the analysis of the results, unless otherwise referenced.

Sara Smith

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LIST OF PUBLICATIONS

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S. Smith, HIM Davidson, DAS Jenkins (2005): Validity of nutritional assessment methods in long term haemodialysis patients. *Proceedings of the Nutrition Society.64 (suppl 1B): 100A.*

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CHAPTER 1: INTRODUCTION

1.1 OVERVIEW OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a long term condition caused by bilateral damage to the kidneys. CKD results in the irreversible loss of the kidney's ability to excrete waste products and to regulate electrolyte and water balance. As such it is a condition known to be associated with a myriad of complications including uraemia, cardiovascular dysfunction, anaemia, protein energy wasting, muscle wasting/ weakness, reduced physical functioning and quality of life (Johansen 2007).

There is no single cause of CKD and all individuals with evidence of persisting kidney damage, ie> 90 days, are defined as having chronic kidney disease (CKD) (SIGN 2008). In the United Kingdom (UK) the causes of CKD are coded and grouped into five categories which recognise the most common causes, namely: glomerulonephritis, interstitial nephritis, diabetic nephropathy, multi-system disorders and unknown diagnosis (SRR 2007). Additionally, in the UK, CKD is categorised according to the level of kidney function (regardless of cause) as defined by the glomerular filtration rate (GFR) and known as stages of CKD with a higher stage representing a lower GFR level (National Kidney Foundation 2002) (Table 1.1).

Individuals with Stage 5 CKD require some form of renal replacement therapy (RRT) to survive. There are three principal modalities of RRT available, namely haemodialysis, peritoneal dialysis and transplantation. Haemodialysis is normally performed in hospital, but can be undertaken in an individual's home and is typically

performed for 4-5 hours, three times a week. Dialysis is often a life long therapy as there are far more individuals with kidney disease than there are donor kidneys. Though life saving, RRT is expensive with an estimated two percent of the total annual NHS budget spent on RRT (NCC-CC 2008). Current mean costs of hospital based HD are £35,023 versus home HD costs of £20,764 per annum (Baboolal et al 2008).

Table 1.1: Stratification of Chronic Kidney Disease.

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or raised GFR	$\geq$ 90
2	Kidney damage with mild decrease in GFR	60-89
3A	Moderately lowered GFR	45-59
3B		30-34
4	Severely lowered GFR	15-29
5*	Kidney failure (end-stage renal disease)	< 15

Source: SIGN 2008. *At stage 5, a suffix of D would indicate that an individual is on dialysis.

The mean prevalence of CKD in the worldwide population is reported as 11% with the size of this population increasing at a rate of 7% per year globally (Lysaght 2002, Coresh et al 2003, Hallan et al 2006). This is primarily due to an increase in known risk factors for the development of CKD, namely older age, hypertension and diabetes (Coresh et al 2003). As a direct consequence of the increasing rise in the prevalence of CKD *per se*, it is also evident from available statistics that there has been a rapid and sustained rise in the number of individuals requiring RRT over the last two decades (SRR 2007). Population projections demonstrate that growth will continue until at least 2030 with the main increase being seen in haemodialysis (BRS 2002). This prediction is also mirrored by the Cross Party Group on Renal

Disease in Scotland who considers that, due to the increasing number of older patients and/or those with significant co-morbidities the largest increase in RRT will be hospital HD (CPG on KD 2004). This is primarily because PD or home HD will be inappropriate or impractical for many older patients and/or those with significant co-morbidities.

1.1.1 Scottish perspective on chronic kidney disease

Mirroring the worldwide increase, the number of patients on RRT in Scotland has risen by 37% over the last 10 years (1758 in 1994, 2793 in 2004). The numbers are also expected to continue to rise as a consequence of the ageing population (Newnhan & Ryan 2002). The primary causes of CKD and reasons for RRT in Scotland are: Multisystem 26%, unknown 22%, interstitial 20%, diabetes 18% and glomerulonephritis 14%. The prevalence of both multisystem and diabetes as primary causes is increasing which in turn is increasing the number of patients with significant co-existing comorbidities.

As expected, the number and proportion of older adults on RRT in Scotland is also increasing year on year, with the median age for new patients starting RRT rising from 24 years in 1964 to 65.3 years in 2004. Patients over 65 years now constitute 52% of patients on RRT in comparison to 0% 24 years ago and the hospital HD population is older with a median age of 65.3 years in comparison to a median age of 56.5 years for PD and 47.9 years for transplant. In 2004, 3,640 patients were receiving RRT; 48% of patients had a functioning kidney transplant, 41% were being treated with haemodialysis (HD) and 11% with peritoneal dialysis (SRR 2007).

Life expectancy for patients receiving RRT in Scotland is significantly less than the general population in Scotland. Median survival for patients receiving RRT (all ages) is 4.5 years (95% CI 4.3-4.7). This decreases with increasing age at the time of starting RRT and is approximately 50% less than the general population (SRR 2007). The excess mortality has been attributed primarily to an increased level of comorbidities and cardiovascular or vascular disease elsewhere which may or may not be caused by, or be the cause of, the renal failure (Khan et al 1993). This was clearly demonstrated by a prospective observational study carried out in Scotland examining mortality and associated risks in dialysis patients which was published in 2003. The study of 523 patients found that mortality after 1 year was 15.8% and 2 year mortality was 32% (excluding deaths within the first 90 days), higher than England, Europe and the USA (Metcalfe et al 2003) and unchanged from figures published 10 years earlier (Khan et al1993). The explanation given for Scotland's mortality figures being higher than the UK average was the higher incidence of older patients with increased comorbidity starting RRT (Metcalfe et al 2003).

In the wider dialysis population, HD patients consistently demonstrate poorer physical functioning than healthy age and gender matched controls and this is associated with a higher mortality (DeOreo 1997, Knight et al 2003, Lowrie et al 2003, O'Hare et al 2003). These poorer levels of physical function are more pronounced in older HD patients than in comparison to age matched controls (Johansen 2000, Knight et al 2003, Sterky & Stegmayr 2005) and have been shown to increase the risk of disability for older HD patients (Altintepe et al 2006). In view of the ageing HD population, this suggests that further demands on healthcare resources are likely as a consequence (Kalantar-Zadeh et al 2001a, Lowrie et al 2003). While less is known about the prevalent Scottish dialysis in this regard, it is

assumed that such findings would be mirrored and that a greater impact on healthcare resources is inevitable.

1.2 PHYSICAL FUNCTIONING IN HAEMODIALYSIS PATIENTS

HD patients consistently demonstrate a poorer level of physical function, a finding which exists even when differences in gender and age are controlled (Samson et al 2000). This suggests that in HD patients factors other than age and gender are influencing function. The most likely factors are the presence of comorbidities (particularly vascular), the effects of the associated dialysis therapy, dialysis vintage, protein energy wasting and inflammation (Khan et al 1993, Rebello et al 1998, Dwyer et al 2002, Chertow et al 2000, Painter 2008).

Evidence from large observational HD studies using self reported methods of physical functioning that consider confounding factors such as age and comorbidity, have shown that poor physical functioning is associated with increased hospitalisation and mortality. One of the first studies to demonstrate this was a prospective 2 year study of 1,000 HD patients (De Oreo 1997) and subsequent studies have also confirmed this. Lowrie et al (2003) who followed up 13,952 prevalent HD patients for six months, showed that self reported physical functioning was consistently associated with hospitalisation and mortality. They also found that with each 1 point increase in the physical component score there was a 2% reduction in mortality. Knight et al (2003) examined 14, 815 prevalent patients at the initiation of haemodialysis and followed them up for 2 years. They demonstrated that self reported physical functioning was independently associated with an increased mortality (Knight et al 2003). As such, the ability to improve physical functioning in HD patients has gained attention and focus.

1.2.1 Overview of physical functioning in HD patients

It has been suggested that physical functioning in HD patients can be assessed by the use of methods which measure exercise capacity, by the use of performance based measures or by the use of self reported measures (Painter et al 2005). Regardless of which method is used, the levels of functioning in HD patients are found to be consistently lower than those of healthy age matched controls (Painter et al 2005).

Studies in HD patients examining exercise capacity commonly use VO_2max or VO_2peak as an indicator of cardiorespiratory power. These studies have shown that HD patients have a reduced VO_2max or VO_2peak approximately 50-65% of predicted values for age and gender matched controls (Johansen 1999, Sietsema et al 2002, Koufaki & Mercer 2006, Ouzouni et al 2009). This level of impairment is either similar or greater when physical performance based measures (gait speed, grip strength, sit to stand, time to climb stairs) are employed, with studies reporting values in the region of 50-85% less than predicted values for age matched controls (Bohannon, Smith & Barnhard 1994, Heimburger 2000, Painter et al 2000a, Painter et al 2000b, Johansen et al 2001, Sterky & Stegmayr 2005). Furthermore, studies of HD patients using self reported methods of physical functioning, have also consistently reported lower levels of functioning, approximately 25-50%, in comparison to age matched controls (Khan et al 1995, De Oreo 1997, Merkus et al 1997, Kutner, Zhang & McClellan 2000, Painter et al 2000a, Allen et al 2002, Diaz-Bux et al 2000, Tawney et al 2000, Lowrie et al 2003, Perlman et al 2005, Stack et al 2005, Altintepe et al 2006).

Biopsies of skeletal muscle from CKD and HD patients have demonstrated a number of abnormalities in structure and function which may explain the reported functional impairment (Table 1.2). It would appear that the cause of these skeletal muscle abnormalities is multifactorial in origin, with physical inactivity (deconditioning), alterations in nutritional status and derangements in clinical status such anaemia, uraemia and inflammation being implicated (Kouidi et al 1998, Franssen, Wouters & Schols 2002, Hung et al 2002).

Table 1.2: Summary of abnormalities in muscle morphology and metabolism

Atrophy of muscle mass; both type I & type II fibres with greater atrophy of type II
Reduction in contractile tissue
Reduction in capillary density and mitochondria
Reduction in mRNA levels for IGF-IEa, IGF-II & IGF-I receptor
Increased fragmentation of mIGFBP-3
Decline in oxidative and anaerobic enzyme activities
Excessive glycogen deposition in fibres

(Diesel et al 1993, Conjard et al 1995, Kouidi et al 1998, Johansen et al 2003a, Kemp et al 2004, Wang et al 2005, McIntyre et al 2006, van den Ham et al 2007)

1.2.2 Physical inactivity and physical function

There is a body of evidence demonstrating that low levels of physical activity in HD patients are common (Zamojska et al 2006, Stack et al 2005, O'Hare et al 2003) and that these levels are significantly lower than that of age matched controls (Johansen et al 2000). In the HD population physical inactivity has been associated with dialysis days (Majchrzak et al 2005), a longer dialysis vintage (Johansen et al 2003b), the female gender and older age (O'Hare et al 2003, Johansen et al 2000).

Physical inactivity has also been associated with lower levels of self reported physical functioning (particularly lower extremity), a higher prevalence of cardiovascular disease (O'Hare et al 2003) and an increased level of all cause and cardiovascular mortality (Stack et al 2005).

Physical inactivity in non-CKD individuals has been reported to result in atrophy of skeletal muscle (particularly type I fibres) secondary to decreased protein synthesis and increased protein degradation along with changes in capillary density and a reduction in muscle oxidative capacity which affect the strength and endurance of existing skeletal muscle (Franssen, Wouters & Schols 2002). As any of these findings are consistent with those reported in CKD and HD patients (Table 1.2), physical inactivity is considered to be an important cause of the functional impairment seen in this group. Therefore, decreasing physical inactivity appears to be key, but addressing other contributory factors such as a loss of fat free mass (FFM), the uraemic state and inflammation could also be important.

1.2.3 Nutritional status and physical function

In non-CKD individuals a prolonged state of negative energy balance resulting in protein energy wasting (PEW) also results in findings which are consistent with many of the abnormalities seen in CKD patients (Table 1.2). Therefore, PEW has been suggested as a contributory cause of poor physical functioning in this group (Franssen, Wouters & Schols 2002). However, in the HD population this is not supported by a broad and consistent body of evidence as the majority of studies examining physical functioning have not controlled for parameters of nutritional status.

From the available evidence, observational studies of HD patients have demonstrated positive associations between physical activity, physical function, exercise capacity and parameters considered to reflect FFM such as serum creatinine and serum albumin (Fahal et al 1997, Johanson et al 2000, Johanson et al 2001, Allen et al 2002, Sietsema et al 2002). However, the use of parameters such as serum albumin is likely to be misleading in determining the role of nutritional status on physical functioning (Futher discussed in section 1.4.1).

Studies examining associations between physical functioning and markers of nutritional status such as body mass index (BMI), have either demonstrated no association (Johansen et al 2000, Johansen et al 2001) or at best a weak association (Zamojska et al 2006). Further to this, numerous other studies of HD patients have demonstrated that significant functional impairment (compared to age matched norms) can exist even in those who would be considered normally nourished (BMI 20-25 kg/m^2) or well nourished/overweight (BMI >25 kg/m^2) (Deligiannis et al 1999, Heimburger et al 2000, Konstantinidou et al 2002, Koufaki, Mercer & Naish 2002a, Headley et al 2002, Kouidi et al 2004, Blake & O'Meara 2004, Macdonald et al 2005, Storer et al 2005, Cheema et al 2007, Kopple et al 2007, van den Ham et al 2007). This does not rule out a relationship between nutritional status and physical functioning, but rather highlights the inappropriateness of BMI as a marker of nutritional status for examining relationships between nutritional status and physical function. This is primarily because BMI is a non-specific nutritional marker that does not differentiate between FFM and FM. Despite this, studies using methods which can differentiate between total FM and FFM, such as bioelectrical impedance analysis (BIA), still fail to confirm the role of nutritional status on physical function. While some studies report a

positive association between FFM and physical functioning (Johansen et al 2001, Zamojska et al 2006) others have not (Johansen et al 2000 & 2003).

Interestingly, in a large observational study of 1, 545 HD patients (Allen et al 2002), although upper arm FFM was not associated with self reported physical functioning, lower limb FFM was (Allen et al 2002). Furthermore, in albeit a small study of HD patents, lower limb FFM was positively associated with physical functioning (Macdonald et al 2005). In addition, another more recent study of HD patients, demonstrated that whilst there was no significant difference in total FFM and FM between HD patients and aged matched controls, HD patients had significantly lower FFM in their lower limbs (Kopple et al 2007). This suggests that consideration of differences in FFM patterning versus total FFM may be important in determining the role of nutritional status in physical functioning.

It can, therefore, be argued that the influence of nutritional status in the physical functioning of HD patients remains largely undetermined, having been hampered by the historical use of unreliable markers of nutritional status and latterly by the lack of consistent evidence.

1.2.4 Clinical status and physical function

Anaemia was considered to be the primary cause of impaired physical functioning in HD patients, prior to the advent of erythropoietin stimulating agents (ESAs) (Daul 2004, Painter 2005). However, in the post ESA era where the correction of haemoglobin to near normal values is possible, it is recognised that other factors such as inactivity, must be influencing function. This is because correcting anaemia improves physical function, but does not return it to normal predicted values (Painter

2005, Akiba et al 2005), suggesting factors beyond the increased delivery of oxygen to muscles. It has also been shown that the administration of ESAs increases serum endothelin levels, which could result in reduced muscle blood flow and may partly explain the limited gains (Carlini et al 1993, Vogel et al 1997). Anaemia however can still be an issue in the HD population and when present, it is associated with disability, decreased physical function, muscle strength and quality of life (Jones et al 2004, Penninx et al 2004, Breiterman-White 2005). Anaemia is now primarily a consequence of hyporesponsiveness to ESAs and one of the known common causes of hyporesponsiveness to ESAs is inflammation (Johnson, Pollock & Macdougall 2007).

Inflammation has also been shown to suppress protein synthesis and/or stimulate protein degradation. Studies in HD patients have demonstrated that higher values of serum inflammatory markers such as CRP and IL-6 are associated with a lower FFM in HD patients (Kaizu et al 2003, Guarnieri et al 2004, McIntyre et al 2006) and that a lower FFM has been found to negatively influence functional ability (McIntyre et al 2006). However, evidence to support a direct, rather than an indirect; effect of inflammation on functioning in HD patients is more ambiguous. Recent studies have failed to show an association between serum inflammatory markers and physical function (Hung et al 2002, Majchrzak et al 2005, Zamojska et al 2006) and deteriorations in physical function have also been observed in the absence of changes in serum cytokine levels (Johansen et al 2003b). On the other hand, it could be argued that due to the inverse association of serum albumin with CRP (Kaysen et al 2000), studies reporting positive associations between serum albumin levels and levels of physical function provide indirect evidence that inflammation is indeed influencing function (Fahal et al 1997, Johansen et al 2000, Johanson et al 2001, Sietsema et al 2002).Despite the ambiguity, the potential contributory

influence of inflammation on physical function is an important consideration, because of its concomitant association with other causes of morbidity and cardiovascular mortality. As such, more work in this area is justified.

Other metabolic and hormonal abnormalities known to exist in CKD are also considered to negatively influence physical function, albeit perhaps to a lesser extent than inflammation. These include acidosis, hyperkalaemia and uraemia, the presence of 'middle molecules' not removed by dialysis, insulin resistance and secondary hyperparathyroidism. In addition, the presence of comorbidities such as vascular disease, side effects of medications such as weakness associated with the use of beta blockers or soft tissue and vascular calcification associated with the use of calcium phosphate binders, have also been implicated (Johansen 1999, Kouidi 2001, Goodman 2003, Siew et al 2007).

1.2.5 Measuring physical function

Maximum oxygen uptake (VO_2max) is considered by many as the gold standard for the measurement of maximum cardiorespiratory power, but its value and use within the CKD population has been questioned, as has the alternative measure of VO_2peak (Mercer et al 1998, Daul et al 2004, Johansen 2005, Painter 2005). This is primarily because a significant proportion of dialysis patients due to their age and comorbidities are unable to perform these tests because of medical concerns and orthopaedic limitations or because of the practicalities and complexities of the testing protocols (Johansen 1999, Painter et al 2000, Moug et al 2003, Painter et al 2005). Furthermore, questions have also been raised regarding the reliability and reproducibility of these tests in older adults (Greig 1994, Greig 2002). As such,

studies in the HD population using this method have been criticised for recruiting only the healthiest dialysis patients (Painter 2005, Johansen 2007).

It has also been proposed that VO_2max does not necessarily reflect a patients' ability to undertake the activities of daily living and may underestimate the extent of functional impairment (Koufaki & Mercer 2006). Moreover, the use of VO_2peak as an outcome measure may not be sensitive to, or in turn may underestimate, improvements in physical functioning (Koufaki, Mercer & Naish 2002a, Johansen 2007). In addition, the tests are costly and impractical to use in the clinical setting. They cannot be performed in the dialysis unit itself thereby creating an additional time burden for patients that may act as a barrier to participation, or contribute to subsequent drop out (Painter, Stewart & Carey 1999).

As an alternative to VO_2peak, it is possible to use measurements that are considered to correlate well with VO_2peak such as the North Staffordshire Royal Infirmary (NSRI) walk test which was validated in a small cohort of both HD and PD patients (Wilcock et al 1998). However, the actual design or space within or around the dialysis unit may preclude the ability to perform such measurements (Painter, Stewart & Carey 1999). Although the measurements could be conducted elsewhere, this also extends the time patients are required to commit, which again could result in a barrier to recruitment and ongoing participation. Evidence from one multicentre study in HD patients supports this, with the findings demonstrating that most clinical areas lack appropriate spaces to perform such tests and that a significant number of patients refuse or are unable to complete such tests thereby limiting their use in longitudinal studies (Painter et al 2000).

The use of other sub maximal physical performance tests such as the sit to stand and timed up and go have been suggested to be a more appropriate and clinically applicable way to assess the effects of exercise interventions in the prevalent CKD population (Painter 2008). Although it is recognised that they are not direct measures of physical fitness, they can be considered indicators (Painter et al 1999). They have also been shown to predict functional dependence, hospitalisation, and mortality in older non-CKD adults (Messier et al 2000). These tests are commonly used in frail older adults (Hoeymans et al 1997, Guralnik et al 1989, Bohannon 2002, Janssen, Bussmann & Stam 2002, Ritchie et al 2005, Nordin et al 2008) and, based on the previously reported low levels of function in HD patients can be considered appropriate for the majority of the prevalent HD population. They do not require extensive equipment or time and do not require the need for skilled professional expertise or training (Podsiadlo & Richardson 1991, Sterky & Stegmayr 2005). They are also considered to simulate activities of daily living and include both upper and lower limb function.

The sit to stand test is considered to be a measure of functional ability and an indicator or proxy of lower limb strength, balance, and mobility (Lord et al 2002). As such it is considered to simulate activities of daily living including getting out of a chair, car or bath, climbing stairs or walking distances (Janssen, Bussman & Stam 2002, Dinan & Skelton 2003). The test is considered to have both convergent construct and discriminate validity. This is justified by its correlation with sit to knee extension force, leg press force and because lower sit to stand scores are reported in older individuals who have low levels of habitual physical activity and who report a higher need for assistance with activities of daily living (Bohannon 2002, Ritchie et al 2005).

Sit to stand performance can either be quantified by the number of repetitions completed in a given period of time or the time taken to perform a set number of repetitions (Bohannon et al 2002). There are several variations of the test such as the sit to stand-5 and the sit to stand-10, where the fastest time to complete 5 or 10 repetitions is recorded. While these versions are considered to be primarily indicators of muscle strength, another variation of the test, the sit to stand-60, is considered to be an indicator of muscle endurance and fatigability. This is because performance is quantified by the number of repetitions which can be completed over a longer period of 60 seconds (Koufaki & Mercer 2006). This version of the sit to stand is increasingly being used in studies conducted within the CKD population (Cappy, Jablonka & Schroeder 1999, Kutner, Zhang & McClellan 2000, Koufaki, Mercer & Naish 2002, Majchrzak et al 2005, McIntyre et al 2006, Majchrzak et al 2007, Cook, MacLaughlin, Macdougall 2008) and has been found to positively correlate with thigh muscle cross sectional area (McIntyre et al 2006). Furthermore the sit to stand-60 has been shown, in a small study of chronic obstructive pulmonary disease patients, to strongly correlate with the distance covered in the six minute walking test and therefore may also provide some indication of exercise capacity (Ozalevli et al 2007).

The 3 metre timed up and go test (TUG) measures in seconds the time taken by an individual to stand up, walk a distance of 3 metres (approx 10 feet), turn and walk back to the chair and sit down. It is considered to simulate and assess in a sequence, functional manoeuvres used in everyday life that involve both motor ability and dynamic balance, such as recovering after tripping and manoeuvring in a crowd (Podsiadlo & Richardson 1991, Bischoff et al 2003, Dinan & Skelton 2003). As such, the test does not focus on independent effects of organ impairments, such as low muscle strength or decreased balance, but measures the interaction of these

factors on the performance of activities of daily living (Bischoff et al 2003). The test is considered to be an objective, reliable, validated test that is quick and easy to perform in the clinical setting (Podsiadlo & Richardson 1991). It has also been shown to positively correlate with the Berg balance scale and the Barthel index and negatively correlate with gait speed (Bischoff et al 2003). Its use as an outcome measure is supported by a growing emphasis on functional capacity of patients This is also reflected in the emerging use of the TUG test in latter studies of the CKD population (Storer et al 2005, Jamal et al 2006, Cook, MacLaughlin, Macdougall 2008).

In summary, it would appear from the literature that the 60 second sit to stand test and the timed up and go test are clinically important and relevant physical performance tests, primarily because they have the advantage of simulating various and multiple activities of daily living associated with lower limb function. Furthermore, both tests have been used within the CKD population and been shown to be sensitive to change as a result of endurance type exercise interventions, including those utlising cycle ergometers (Cappy, Jablonka & Schroeder 1999, Koufaki, Mercer & Naish 2002, Storer et al 2005, Cook, MacLaughlin & Macdougall 2008). Additionally, it would appear that these tests can be easily and efficiently measured within the dialysis setting, thereby minimising the burden on patients and reducing the risk of more complex and time consuming tests acting as barriers to ongoing participation. Furthermore they do not; require extensive specialist equipment or administration by specialist personnel and could therefore potentially be used by dialysis staff to monitor changes in function overtime.

Handgrip dynamometry (HGD) is considered to quantitatively measure muscle strength. Its use as a functional test in older adults provides an indication of the

ability to perform activities of living such as opening containers, lifting weights and the ability to hold onto handrails to climb stairs (Skelton et al 1994). It is considered to be an inexpensive test that is also easy and quick to perform (Bohannon, Smith & Barnhard 1994, Heimburger et al 2000) and latterly the greater use of this test in CKD research studies has been recommended (Fouque et al 2007). Whilst handgrip dynamometry is limited to the measurement of a single task it has been suggested that it can be used to characterise overall muscle strength and has been used in epidemiological studies of healthy individuals as an indicator of overall muscle strength (Bohannon 1998, Rantanen 2003). The use of handgrip as an indicator of overall muscle strength is a feasible model supported by significant positive correlations with other measures of strength such as elbow flexion, knee extension, trunk extension and trunk flexion (Bohannon 1998, Rantanen 2003). Handgrip strength (HGS) has also been found in several studies of older non-CKD patients and CKD populations to predict disability, cardiovascular mortality and all cause mortality (Al Snih et al 2002, Qureshi et al 2002, Rantanen et al 2003). Furthermore, studies involving both healthy subjects and CKD patients have shown that handgrip strength is directly proportional to, and positively correlates with, fat free mass (Heimburger et al 2000, Newman et al 2003, Wang et al 2005).

However, although HGS is positively correlated with FFM and as such is considered to be a major factor in determining handgrip, it is not the only factor. This is because HGS can be altered in the presence of what would be considered a normal nutritional status (BMI) (Martin, Neale & Elia 1985, Heimburger et al 2000) and improvements in HGS can occur without changes in FFM volume, as observed in refeeding situations (Vernon & Hill 1998). As such, evidence from studies in both the non- CKD and CKD population suggests that the functionality of the muscle itself

may be more important than muscle size in determining handgrip and survival (Wang et al 2005, Gale et al 2006).

Factors shown to negatively influence handgrip strength in both the non-CKD population and CKD population include inflammation (Qureshi et al 2002, Rantanen et al 2003, Wang et al 2005, Hamer & Molloy 2009, Schaap et al 2009), insulin resistance (Lazarus, Sparrow & Weiss 1997), arterial stiffness (Gu et al 2008), low levels of IGF-1 (Qureshi et al 1998, Barbieri et al 2003) and low levels of physical activity (Kuh et al 2005). These associations may in turn explain the association between handgrip and mortality and as such justify the use of HGS as an appropriate and relevant outcome measure in exercise intervention studies utlising aerobic endurance type interventions of either upper or lower limbs.

It is also possible to make an assessment of functional status by the use of self reported measurements (eg questionnaires). Furthermore there is a small body of evidence in the HD population suggesting that perceived levels of function reflect and may correlate with objective functional status. Painter et al (2000a) found that those HD patients reporting high levels of physical function, performed better on all objective physical functioning tests. Kutner, Zhang & McClellan (2000) in a study of HD & PD patients found that higher self reported physical function scores were positively associated with levels of physical activity and objective physical performance measures of sit to stand and time taken to walk 20 feet.

Although self-reported measurements are not considered as reproducible or reliable as objective methods (Guranlik et al 1989) these methods have been used as an outcome measure in studies of HD patients to examine patient perceptions and provide a holistic overview of the effects of different interventions (Painter et al

2000a, Johansen et al 2003b). In addition self reported physical functioning has been found to be highly predictive of outcome in HD patients (Painter et al 2000). Furthermore, depending on the measure used, they provide not only evidence of physical dysfunction, but of overall quality of life including psychosocial well being, which is considered to be an important outcome in older, comorbid groups such as the current prevalent HD population (De Santo et al 2008) Therefore the use of self reported function as an outcome measure in exercise intervention studies alongside objective measures of function is justified.

1.3 QUALITY OF LIFE IN HAEMODIALYSIS PATIENTS

Worldwide, studies comparing the dialysis population to the general population have consistently demonstrated that dialysis patients of all ages report a poorer quality of life in comparison to healthy controls or norm based scores (Kutner et al 2000b, Lamping et al 2000, Diaz-Buxo et al 2000, Allen et al 2002, Dwyer et al 2002, Knight et al 2003, Lowrie et al 2003, Perlman et al 2005, Altintepe et al 2006).

Evidence indicates that HD patients perceive their physical quality of life as being worse than their psychosocial (mental) quality of life, with their psychosocial quality of life closer to, and not always significantly different from, population norms. A perception that appears to apply more to older HD patients than younger HD patients (De Oro 1997, Diaz-Buxo et al 2000, Kutner et al 2000b, Lamping et al 2000, Tawney et al 2000, Mittal et al 2001, Allen et al 2002, Dwyer et al 2002, Lowrie et al; 2003, Knight et al 2003, Perlman et al 2005). Some studies, but not all, have also shown that HD patients have a poorer quality of life than PD patients or transplant patients (Merkus et al 1997, Diaz-Buxo et al 2000).

Few studies examining quality of life in CKD patients have been conducted in Europe or the UK. Those that have suggest that patients also report poorer levels of physical function than population norms (Blake et al 2000, Lamping et al 2000, Cleary & Drenman 2004) and may (Blake et al 2000) or may not (Lamping et al 2000, Cleary & Drenman 2004) report a poorer psychosocial quality of life. One study conducted in Scotland demonstrated that patients receiving HD or PD had both a lower physical and psychosocial quality of life than transplanted patients and a sample of the general population (Khan et al 1995).

Reasons for the reported differences in quality of life include the presence of comorbidities (Khan et al 1995, Merkus et al 1997, Diaz-Buxo et al 2000, Dwyer et al 2002), advancing age (Diaz-Buxo et al 2000), dialysis vintage (Rebello et al 1998), the presence of anaemia (Rebollo et al 1998, Kalantar-Zadeh et al 2001a, Perlman et al 2005) and low levels of physical activity (Kutner et al 2000, O'Hare et al 2003). Nutritional status has also been implicated in quality of life. In two observational studies of different HD populations by the same group, significant, but weak negative correlations with BMI and percentage body fat were found (Kalantar-Zadeh et al 2001a, Kalantar-Zadeh et al 2006). Subjective global assessment (SGA), mid arm muscle circumference (MAMC) and serum albumin have also been found to positively correlate with quality of life (Laws et al 2000). Furthermore, in a large observational study of 1,545 HD patients, both calf circumference and serum creatinine were positively associated with perceived physical quality of life (Allen et al 2002). In addition, given that several large studies have found that both a poor psychosocial and physical self reported quality of life are associated with more frequent hospitalisation and increased mortality risk, interventions that improve quality of life may also have wider implications and therefore justifies the inclusion of

quality life as an outcome measure (DeOreo 1997, Kalantar-Zadeh et al 2001a, Knight et al 2003, Lowrie et al 2003, Mapes et al 2004).

1.3.1 Measuring quality of life

Although there is a lack of agreement in the literature regarding the concept of health related quality of life, it is commonly viewed as a multidimensional concept encompassing physical, psychological and social functioning, and a number of questionnaires have been developed on this premise (Kutner 1994, Cleary & Drennan 2005).

In the majority of CKD studies the short form 36 (SF36) generic questionnaire has been utilised (Rettig et al 1997, Khan et al 1995, Blake et al 2000, Kutner et al 2000b, Lamping et al 2000, Diaz-Buxo et al 2000, Mittal et al 2001, Allen et al 2002, Dwyer et al 2002, Johansen et al 2003b, Knight et al 2003, Lowrie et al 2003, Cleary & Drenman 2004, Burrowes et al 2005, Perlman et al 2005, Altintepe et al 2006). While the kidney disease quality of life short form (KDQOL-SF), a disease specific questionnaire for dialysis patients exists, which incorporates the SF36 dimensions, it is more complex and takes twice the amount of time to complete (Phillips, Davies & White 2001). In addition, it has not been widely used in intervention studies of function and quality of life in HD patients.

Whilst the SF36 is a generic questionnaire and not specific to HD patients, it is considered to have construct validity in a range of patient groups including CKD (Brazier et al 1992, Garratt, Ruta & Abdalla1993, Neto et al 2000). Evidence also suggests that the SF36 is suitable for self administration within 5 to10 minutes and has a high degree of acceptability in the general population, as well as European,

UK and Scottish renal populations of various ages (Khan et al 1995, Blake et al 2000, Lamping 2000, Cleary & Drenman 2004).

The SF36 provides a profile of two health component summary measures, the physical component score (PCS) and the mental component score (MCS). It also provides information on eight health domain scales which are, physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Whilst the PCS & MCS are considered to provide a reliable, valid and broad overview of perceived physical and psychosocial morbidity, the domain scales provide information on specific aspects of physical and psychosocial well being which may or may not be similarly affected as a consequence of disease or interventions (Ware et al 2007).

The MH, RE and SF domains and the MCS have been shown to be the most valid of the SF-36 scales for measuring mental health in both cross cultural and longitudinal studies. The PF, RP and BP domains of the PCS have been shown to be the most valid SF-36 scales for measuring physical health. Further to this, the PF scale has been shown to be the best all round valid measure of physical health and the MH scale has been shown to be the most valid measure of mental health in studies to date (Ware et al 2007).

Reliability testing of the SF36 has been reported over a wide range of conditions including HD. In a HD population the internal consistency of the eight domain scales ranges from 0.82 and 0.92, which compares favourably with reported internal consistency for other populations (Cleary & Drennan 2004).The SF-36v2, the later improved version of the original short form-36 is easier to understand and complete. It is considered to have comparable reliability and validity and it is this version that is

now recommended for use. However, the use of norm based scores allows ongoing comparability between studies using the SF-36 (Ware et al 2007).

1.4 NUTRITIONAL STATUS IN HAEMODIALYSIS PATIENTS

Previous studies in HD patients have reported a wide prevalence of protein energy wasting (PEW) of between 18-75% (Kalantar-Zadeh & Kopple 2001). Multiple causes of PEW in HD patients have been suggested, including poor dietary intakes secondary to a loss of appetite, catabolism secondary to the dialysis process, under dialysis, metabolic acidosis, chronic inflammation and hormonal derangements (Ikizler et al 2002, Sanaka 2003, Guarnieri et al 2004, Carrero et al 2007, Dong & Ikilzer 2009).

Nutritional status is likely to influence physical function and quality of life in HD patients, but it also appears from observational studies that there is a strong independent relationship between PEW (defined by low serum albumin) and mortality risk in HD patients (Kovesdy & Kalantar-Zadeh 2009, Lacson, Owen & Lowrie 2000). However, the pathophysiological mechanism by which PEW causes an increased mortality in HD, particularly from cardiovascular disease is not completely understood (Kalantar-Zadeh & Kopple 2001). Nevertheless, it has been intimated that the association of PEW and cardiovascular disease with active inflammation may be the link (Bergstrom & Lindholm 2000, Kaysen 2000, Avesani et al 2006).

It should be emphasised however, that determining the role of PEW in mortality is complicated by the majority of previous studies using serum albumin or subjective global assessment (SGA) to identify PEW and predict mortality risk (Qureshi et al

1998, Leavey et al 1998, Heimburger et al 2000, Pifer et al 2002, Pupim et al 2004a). These measures are likely to be misleading in the contribution of nutritional status versus inflammation to mortality. Therefore, the continued use of these markers is likely to confound the ability to recognise the true causes of increased mortality and potentially hinder appropriate interventions as a consequence (Barbosa-Silva 2008). This view has been borne out in two observational studies of HD patients. One study demonstrated that body weight and body mass index did not correlate with serum albumin and C-reactive protein levels and in turn they did not predict mortality (Kimmel et al 2003). Another recent observational study examining the impact of PEW on mortality, which used markers of FM and FFM alongside serum albumin and a scoring system similar to SGA, found that after adjusting for age and gender, the presence of comorbid conditions and CRP were the only significant predictors of mortality (Stojanovic et al 2008). Furthermore, while a few studies examining changes in body composition of HD patients over time (Ishimura et al 2001, Jager 2001); suggest that FM increases and FFM decreases, the relationship of these changes with quality of life, functional status and clinical status have not been examined in the current prevalent HD population.

1.4.1 Measuring nutritional status

The body is not one homogenous compartment, but is composed of several compartments, which are targeted and affected differently by inflammation and/or PEW. As a consequence, interventions in the presence of inflammation and/or PEW are likely to vary in their effects on these compartments and it is therefore important to understand and differentiate between them (Locatelli et al 2002).

Figure 1.1 depicts the major components of body weight and the different measurable compartments. At the simplest level, body weight can be divided into two compartments, FM and FFM. FFM can be divided into several compartments, including body cell mass (BCM), intracellular water (ICW), extracellular water (ECW) and bone mineral (Roubenoff 1999).

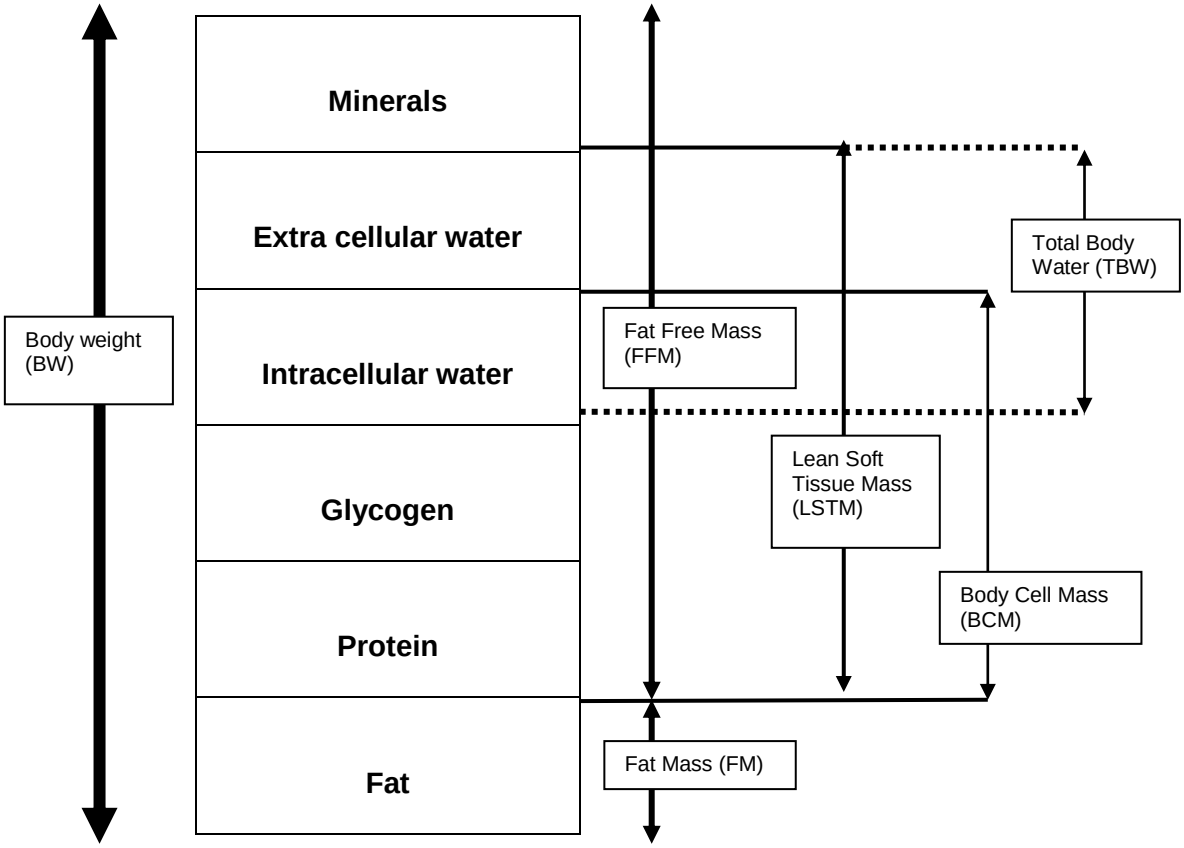


Figure 1.1: Components of body weight (adapted from Kyle 2004, Cano et al 2009)

Due to the nature of CKD, an increase in total body water (TBW) and body weight occurs with a concomitant expansion of ECW volume between dialysis sessions, which is then corrected via the dialysis process (by the ultrafiltrate volume). Any increases in TBW can therefore lead to an overestimate of FFM, and/or mask

significant losses. This therefore requires consideration in the assessment and serial monitoring HD patients.

Several methods of assessment, although considered to have high degree of accuracy, are expensive, not routinely available, time consuming, uncomfortable for older patients making it difficult for them to co-operate, require skilled operators, expose patients to unacceptably high levels of radiation and are not practical for longitudinal monitoring of patients (Jebb & Elia 1993). These include densitometry, near infrared interactance, *in vivo* neutron activation analysis (IVNA) and imaging techniques such as computed tomography, magnetic resonance imaging or ultrasound scanning. As such, their use in CKD is limited and the validity of many of these techniques in CKD patients is largely unknown (Kalantar-Zadeh et al 2001b, Pupim & Ikizler 2004, Kamimura et al 2005).

One method, dual energy x-ray absorbitometry (DXA) is increasingly being used as a reference method in preference to densitometry or IVNA (Pietrobelli et al 1998, Kamimura et al 2005, Sundell, Pupim & Ikilzer 2007) and is considered reliable and superior to other non-invasive methods in HD patients (Devita & Stall 1999, Locatelli 2002).This method was originally developed for the measurement of bone density and bone mass, but subsequent developments in technology have allowed the quantification and differentiation of soft tissue mass. DXA is able to determine three compartments of body composition, lean soft tissue mass (LSTM), bone mineral content (BMC) (LSTM + BMC= FFM) and FM at a whole body or a regional level. However, it is not without some limitations; although the method requires minimal time and exposes individuals to low levels of radiation, it does still require a skilled operator, it is expensive and not routinely available for nutritional assessment purposes and as such limits it use in longitudinal studies (Kamimura et al 2005).

In the clinical setting, subjective global assessment (SGA) has frequently been used in the CKD population and is considered by many as a simple, safe and inexpensive measurement of nutritional status (Barbosa-Silva & Barros 2006). It involves the 'judgement' of protein energy wasting (PEW) by several markers and is based on clinical history and physical examination only with no anthropometric measurements or biochemical measurements. It has been commonly used to quantify the prevalence of PEW in CKD patients and has also been used for assessment and monitoring purposes. However, there is a growing body of evidence that highlights the limitations of SGA. The evidence highlights that as SGA is largely subjective its sensitivity, precision and reproducibility may be insufficient to detect the presence of PEW or small acute changes in nutritional status over time in HD patients (Cooper et al 2002, Jones, Wolfendale & Wells 2004, Bossola et al 2005). It has been suggested that instead it is a marker of overall 'sickness' or general well being as at a diagnostic level it is likely to be detecting not only the presence of PEW , but also inflammation and its severity (Kalantar-Zadeh & Kopple 2001, Jones, Wolfendale & Wells 2004, Barbosa-Silva & Barros 2006). This is not advantageous when trying to identify causes of PEW (inflammation driven versus reduced intake), or when determining the effectiveness of specific interventions (Kalantar-Zadeh et al 2003).

Serum albumin has been another frequently used measure of nutritional status in the CKD population, with its use based on the concept that levels directly reflect visceral protein stores. Whilst this is true to an extent, many other factors influence the generation, distribution between intravascular and extravascular spaces, and catabolism of albumin. These factors include albumin synthesis inhibition secondary to acidosis or inflammation, exogenous albumin losses across dialysis membrane or dilution due to over hydration (Yeun & Kaysen 1998, Dumler 2002, Jones et al 2002, Cigarran et al 2007). Futhermore, in CKD, it has been shown that serum albumin

has no relationship with FFM stores (Dumler et al 1997, Heimburger et al 2000) and that in HD, levels do not differ significantly between well nourished and malnourished patients (Cooper et al 2002, Dos Santos et al 2003, Jones, Wolfendale & Wells 2004, Desbrow et al 2005). This has led to the recent view that serum albumin has been, and continues to be, erroneously used as a nutritional marker and that it should no longer be considered as such, but rather as an inflammatory marker (Barbosa-Silva 2008). Therefore, similar to SGA, its use in the diagnosis of malnutrition and in determining the effectiveness of interventions on nutritional status is limited (Kliger 2002).

Despite its poor specificity and inability to differentiate between FFM and FM, body mass index (BMI) is another frequently used measure of nutritional status in the CKD population (Axelsson et al 2005, Mafra & Foque et al 2008). While some studies in CKD patients have suggested that a higher BMI confers morbidity and mortality advantages not seen in the general population (Kopple et al 1999, Fleischmann et al 1999), these studies did not examine FFM or FM. Subsequent studies, including a large retrospective, observational study of 70,028 patients, have suggested that the protective effect from a high BMI is only conferred upon patients with a normal or high muscle mass and that patients with a high BMI secondary to a high body FM have an increased, rather than a decreased mortality (Beddhu et al 2003). This has also been seen in other studies, suggesting that the preservation of FFM rather than body mass *per se* is key. One such study in HD, which examined the influence of body composition on 5 year mortality, found that BMI did not influence mortality in either gender, but that a significant reduction in FFM negatively influenced mortality in men (Kato et al 2003). In another study which followed 344 HD patients for 10 years, patients with BMI's < 25kg/m^2 and with an adequate mid arm muscle circumference (MAMC) had lower mortality rates than those with BMI >

25 kg/m^2 and a low MAMC (De Araujo et al 2006). As a consequence of this evidence, it has recently been suggested that studies should examine FFM and FM stores in preference to BMI (Marfa & Fouque 2008).

Measurement of limb circumferences and skinfolds are the least expensive methods of nutritional assessment that when used together can differentiate between FM and FFM (Pietrobelli et al 1998, Fouque et al 2007, Sundell, Pupim & Ikizler et al 2007). Commonly, circumferences and skinfolds of upper limbs at single sites, particularly the tricep, are used due to accessibility and ease in clinical practice and are deemed useful to track long term changes in nutritional status (Pichard & Kyle 1998, Pupim & Ikilzer 2004, Fouque et al 2007). Although inter and intra observer variability in untrained individuals can be high; the use of a single trained observer, appropriate equipment and standardised protocols overcome this (Jebb & Elia 1993, Norton & Olds 1996).

In the CKD population a higher mid arm circumference (MAC) has been associated with reduced mortality (Dwyer et al 2005) and MAMC has been shown to have a strong correlation with IGF-1 (Qureshi et al 1998). Such measurements have also been considered to provide reliable markers of total body FFM and FM status, but little validation work, particularly in the HD population, has been done to support this.

The use of lower limb circumferences and skin folds such as calf has been uncommon until recent years, but data is emerging that these particular measurements may be of clinical value. In older non- CKD populations, calf circumference (CC) has demonstrated a positive correlation with skeletal appendicular mass, and a calf circumference of <31cm has been negatively

associated with disability and self reported physical function, independent of age and comorbidity in women (Rolland et al 2003). More recently, a small CC (<33cm) has also been positively associated with carotid plaques (Debette et al 2008). Furthermore, when calf circumference and calf skinfold measurements have been used together to estimate calf muscle circumference (CMC), a small CMC (<29cm) has been shown to be positively associated with a risk of falling in women (Stewart, Stewart & Reid 2002).

The use of lower limb measurements in the CKD population is also emerging (Allen et al 2002). Data from one large study of 1,545 HD patients conducted in the USA, demonstrated that CC was independently and positively associated with self reported physical function (Allen et al 2002), subjective ratings of appetite (Burrowes et al 2005) and that a small CC (<31 cm) may be positively associated with mortality (Dwyer et al 2005). However, the relationship of these measurements with total body FFM stores in both the non-CKD population and the CKD population does not appear to have been examined.

Another method of assessment that is gaining increasing popularity and acceptance in the CKD population is bioelectrical impedance analysis (BIA). Although it was initially used more commonly in the management of hydration status in HD, it is increasingly being used as a method for assessing nutritional status and is considered a simple, practical, time efficient bedside tool (Ho et al 1994, Jaeger & Mehta 1999, Chamney et al 2002, van de Kerkhof et al 2004, Barbosa-Silva 2008). BIA is the only clinical method available that can potentially, depending on the frequency used, estimate total body water (TBW), extracellular water (ECW), intracellular water (ICW), fat free mass (FFM), body cell mass (BCM) and fat mass (FM), at a whole body level and is considered to have less intra observer error than

skinfold thickness (Jebb & Elia 1993). Such a method is, therefore, likely to provide a greater understanding of potential changes in whole body composition in the HD population.

BIA monitors which use a monofrequency of 50 kHz, have been commonly used in HD patients, but are limited by their inability to reliably measure ECW and to differentiate between ECW and ICW, thereby allowing less accurate estimates of FFM, FM and body cell mass. Although newer dual frequency and multifrequency monitors are now available, which can differentiate between ECW and ICW, their use in the HD population has been limited and validation work is therefore required prior to use in this population.

Protein and energy requirements are considered to be greater in HD patients than in healthy individuals secondary to a number of disease specific causes such as dialytic losses of amino acids, metabolic acidosis and comorbid conditions such as chronic systemic inflammation and infections. Recommendations and guidelines consistently suggest that HD patients require 30-40kcal/kg/IBW/day and 1.2g of protein/kg/IBW/day to meet requirements (Fouque et al 2007). However, studies have demonstrated that actual intakes are often less than these recommendations with energy intakes commonly reported to be approximately 25kcal/kg/day and protein intakes 0.7-1.0g/kg/day and, as such, are considered an important cause of PEW in CKD patients (Bossola et al 2005). Furthermore, evidence from a large multicentred study in the USA suggests that dietary intakes on dialysis days differ significantly from intakes on non dialysis days, with intakes of energy and protein being significantly higher on non dialysis days than dialysis days (Burrowes et al 2003).

In CKD patients a decreased dietary intake is likely to be caused by poor appetite (motivation to eat) which is multifactorial in origin. The likely causes of poor appetite in HD patients are uraemic dysgeusia, the dialysis process (inadequate dialysis dose, effect of dialysis membrane, post dialysis fatigue and cardiovascular instability), dialysis vintage, systemic inflammation, inappropriate dietary restrictions, psychological factors, medications, impaired odour perception and older age (Griep et al 1997, Reilla et al 2000, Burrowes et al 2002, Ikizler et al 2002, Carrero et al 2007, Zabel et al 2009a).Evidence suggests disturbances of appetite in CKD patients are common and that these are greater on dialysis days than on non-dialysis days (Wright et al 2001) and in turn there is a body of evidence which suggests poor appetites are associated with a poorer morbidity and mortality in HD patients. In a study of 331 maintenance HD patients, 38% of patients reported a diminished appetite (fair to poor), which was associated with higher concentrations of proinflammatory cytokines (including hsCRP), unresponsiveness to ESAs, poor clinical outcomes (increased mortality, greater hospitalisation) and a poorer quality of life (Kalantar-Zadeh et al 2004). In addition, data from 1,846 HD patients analysed as part of recruitment to a long term prospective study of dialysis adequacy, demonstrated that a poor appetite at baseline was significantly and negatively associated with a number of parameters such as BMI, calf circumference, quality of life, normalised protein catabolic rate (nPCR) , energy and protein intakes (Burrowes et al 2005). This is further supported by a more recent study which found that poor appetite was positively associated with low nPCR levels, poorer outcomes (even after adjustment for comorbidity), longer dialysis vintage , increased inflammation, lower haemoglobin, and a higher mortality risk (Lopes et al 2007).

There are several methods for measuring dietary intake, with the most commonly used being twenty four hour recalls or two to seven day food record diaries (weighed

or unweighed). Recalling what a patient has consumed over the previous twenty four hours is considered a simple method, which can highlight major imbalances, obvious dietary inadequacies or highlight areas of concern, but its reliance on memory may create difficulties for older adults and it may also underestimate intake, or not be representative of, an individual's typical intake (Fouque et al 2007). In patients with a stable intake such as the majority of HD patients, a food diary for a period of less than seven days, such as two to three days, may be adequate to assess protein and energy intake (Fouque et al 2007), but is unlikely to be of sufficient duration to reliably and accurately assess micronutrient intakes. In studies of HD patients a variety of methods for measuring dietary intakes have been used, but in a large long term multicentre haemodialysis study in the US, the preference was for a two day diet diary (included one dialysis day and one non-dialysis day) to examine changes in dietary protein and energy intakes over time (Burrowes et al 2003).

Serial protein intakes can also be measured by the use of protein catabolic rate (PCR) derived from urea kinetics. HD patients do not excrete significant amounts of urinary nitrogen and therefore the rate of increase in serum urea levels between two dialysis sessions is a reliable indication of dietary protein intake (National Kidney Foundation 2000). This indirect measure is calculated via the urea-kinetic method and known as protein nitrogen appearance rate or protein catabolic rate (PCR). However, PCR is not without limitations; in catabolic patients PCR will exceed protein intake to the degree of body protein catabolism and conversely in anabolic patients PCR will underestimate actual protein intake (Cano et al 2009). In addition as there is a day to day variation in protein intake, a single PCR measurement may not reflect usual protein intakes (Kamimura et al 2005). Despite the limitations associated with PCR, it is considered to be a reliable surrogate of dietary protein

intake, providing a more accurate less time consuming estimate of dietary protein intake than obtained from dietary recall/diaries, (Shinaberger et al 2006). In addition, it is one of the monthly reported parameters in many dialysis centres and is therefore readily available.

Disturbances in appetite have been assessed in HD studies using a variety of techniques, however the majority of studies in CKD patients, including the largest to date (Burrowes et al 2005), have utilised the appetite and diet assessment tool (ADAT). The ADAT is a 44-item self administered questionnaire which retrospectively explores general levels of appetite, eating habits and differences between dialysis and non-dialysis days. However, its completion is time consuming and it is unclear whether the ADAT is able to detect changes in dietary habits and appetite, thereby limiting its use in longitudinal studies (Burrowes et al 2003).

More recently, in the CKD population, visual analogue scales (VAS), either paper based or electronic, have been used to prospectively examine subjective sensations of hunger, satiety, fullness and desire to eat (Wright et al 2001, Wright et al 2003, Zabel et al 2009a). A VAS is typically a 100mm line with words anchored at each end, expressing the most negative and most positive ratings (Flint et al 2000). They are considered to be more sensitive and less restrictive than category scales (Likert scales) which may be a source of bias. Furthermore, VAS are quickly and easily scored and such scales are now a well established method for measuring various subjective sensations and desires of appetite (Stubbs et al 2000). Although one concern when using a VAS is the need to standardise external factors that can influence sensations and desires such as prior meals, a small study of healthy men suggests that VAS are reliable and not influenced by prior diet standardisation (Flint et al 2000). Additionally, appetite VAS are considered to show some ability to predict

aspects of feeding behaviour and to act as a useful adjunct to measures of food, energy and nutrient intake. They are also sensitive to experimental manipulations, provided those manipulations exceed or disrupt the effects of conditioned motivation to eat (eg hunger at meal times). In addition they show good reproducibility under controlled conditions provided that they are used in within-subject designs, and provided that the same system eg pen and paper versus electronic appetite rating systems are not used interchangeably (Stubbs et al 2000, Zabel et al 2009b).In summary, it is apparent that there is no definitive single method available in clinical practice to assess nutritional status or responses to interventions overtime that can be considered a 'gold standard'. It therefore seems prudent to use a number of methods concomitantly. From the literature it would appear that appropriate outcome measures in clinical practice include those of body composition allowing the quantification of FM versus FFM such as limb circumferences, skinfolds and BIA along with those that can reliably, but easily quantify appetite and dietary intake such as VAS, food diaries and PCR.

1.5 CLINICAL STATUS IN HAEMODIALYSIS PATIENTS

It is now well recognised that CKD is associated with a chronic low grade inflammatory state interspersed with episodes of acute high grade inflammation (Kaysen 2000, Wessels & Moldawer 2000, Pupim, Flakoll & Ikilzer 2004, Yao et al 2004) and it has been reported that between 30-65% of HD patients show signs of inflammation (Steinvenkel & Alvestrand 2002, Del Vecchio et al 2005).

The causes of inflammation in the HD population are multifactorial and likely to vary between patients, with reduced renal clearance, accumulation of advanced glycation end products, genetic predisposition, gender, older age, presence of non-functioning

arteriovenous fistulas, failed kidney transplants, bacterial or viral infections along with the presence of other inflammatory comorbid conditions all being implicated (Steinvenkel & Alvestrand 2002, Kaysen & Kumar 2003, Del Vecchio et al 2005, Guarnieri et al 2004, Lopez-Gomez et al 2004).

The kidney is an organ that excretes cytokine metabolites and contributes to the cytokine production via its endocrine functions; therefore both decreased renal clearance and increased synthesis of cytokines contribute to the chronic inflammatory state seen in CKD (Pecoits-Filho et al 2003, Yao et al 2004). Moreover, in HD patients the dialysis procedure itself is also considered to contribute to the observed chronic inflammatory state through blood contamination from end toxins in the dialysis fluids and repeated contact of blood with artificial materials such as the dialyser membrane (Sitter, Bergner, Schiffl 2000, Pupim, Flakoll, Ikilzer 2004, Yao et al 2004) and, as such, stimulates the production of cytokines during the dialysis process itself (Rysz et al 2006, Korevaar et al 2004). Because of these known effects, the measurement of high sensitivity CRP (hsCRP) in the HD population has become standard practice and used to indicate the presence of inflammation and/or cardiovascular risk (Ridker 2001). This is because the use of hsCRP is considered to be a good inexpensive marker of inflammation, showing similar behaviour to and, as such, reflecting the generation of IL-6, IL-1, TNF-α and is a known independent predictor of serum albumin (Qureshi et al 1998, Kaysen et al 2000, Steinvenkel & Alvestrand 2002, Kaizu et al 2003, Lacson & Levin 2004).

The effects of an inflammatory state are also multifactorial. In addition to its potential effects on function and FFM, it has been shown that elevated cytokine levels consistently predict mortality, superseding hypoalbuminaemia (Yeun & Kaysen

1998, Ikizler et al 1999, Zhang et al 2004, Regidor et al 2006). It is thought that the ability of CRP to predict mortality lies in its significant contribution to atherosclerotic cardiovascular disease, which is still the most common cause of mortality in the dialysis population (Yao et al 2004). As previously stated, inflammation has also been shown to be a strong predictor of resistance to erythropoietin, with inflammation shown to negatively correlate with the ESA dose required (Barany et al 1997, Gunnell et al 1999, Kalantar-Zadeh et al 2003, Locatelli et al 2006). Therefore, interventions which may modulate the production of cytokines could have significant potential in influencing several outcomes in the HD population.

As highlighted previously, systemic inflammation is known to suppress appetite (Hung et al 2002, Kalantar-Zadeh et al 2004). One explanation for how cytokines may suppress appetite is via a leptin mediated pathway. Leptin is an adipocyte derived hormone considered to be an important signal of appetite control and to be a regulator of food intake and energy homeostasis (Mak et al 2006, Scholze et al 2007). In healthy individuals with normal renal function leptin secretion by the adipocytes reflects FM stores and leptin levels positively correlate with body weight, insulin levels and cytokine activity (Norton 2002).

In CKD and HD patients, hyperleptinaemia is a common and consistent finding, along with a higher leptin to FM ratio than is seen in healthy individuals (Johansen, Mulligan & Schambelan 1998, Nishikawa et al 1999, Norton 2002, Bossola et al 2004, Wright et al 2004, Mak et al 2006). This is thought to be due in part to the decreased renal clearance of leptin shown by the inverse correlation between creatinine clearance and leptin concentrations. It is also thought to be due to the inability of the HD process to effectively remove circulating leptin (Stenvinkel 1999, Zoccali et al 2005, Mak et al 2006) and the possibility that the HD process further

stimulates leptin production by an inflammatory mediated pathway (Dashti et al 2008). Therefore, inflammation may stimulate leptin synthesis and secretion. In turn it has been speculated that a hyperleptinaemic state could be the cause of the appetite inhibition and poor dietary intakes, but the picture in HD is conflicting (Stenvinkel 1999). From the small body of evidence available some observational studies have demonstrated a positive correlation between leptin levels and cytokine levels in HD patients (Pecoits-Filho et al 2002, Axelsson et al 2005, Zoccali et al 2005) while others have not (Don et al 2001, Bossola et al 2004). Some observational studies have shown an association between leptin levels, appetite or poor intakes and lower FFM (Young et al 1997, Johansen et al 1998), whilst others have not (Bossola et al 2004, Wright et al 2004, Zabel et al 2009b). What is clear from the existing literature is that the relationship of leptin with appetite, dietary intakes, inflammation and clinical status has not been prospectively examined over time and as such the role of leptin remains largely undetermined. Therefore, further work in this area is required.

1.6 EXERCISE AS AN INTERVENTION TO IMPROVE PHYSICAL FUNCTION, QUALITY OF LIFE, NUTRITIONAL AND CLINICAL STATUS IN HD PATIENTS

Over 30 years ago exercise interventions in the HD population first attempted to improve or provide cardiovascular benefit (Goldberg et al 1979). Latterly the intention has been to not only provide cardiovascular benefit, but functional, quality of life, nutritional and clinical benefits (Painter et al 2002, Macdonald et al 2005, Kopple et al 2007, Ouzouni et al 2009). These exercise interventions have either been aerobic, resistance or combined aerobic and resistance, with aerobic exercise considered to primarily improve cardiorespiratory endurance, and resistance exercise to primarily improve muscular strength and endurance (American College

of Sports Medicine 2000). However, there are a number of methodological limitations that have, to date, prevented exercise being advocated as part of routine care.

A search of the literature from January 1979 up to February 2009, using electronic databases (CINAHL, PubMed, Ovid, Cochrane Library) and limited to the English language, was undertaken to identify previous exercise studies of the HD population that focused on functional, quality of life, nutritional and clinical outcomes. From this search, it would appear that whilst a small number of studies have used resistance type interventions (Headley et al 2002, Nindl et al 2004, Cheema et al 2007a & b) or combined resistance and aerobic interventions (Deligiannis et al 1999, Deligiannis , Kouidi , Tourkantonis 1999, Ridley, Hoey, Ballagh-Howes 1999, Cappy, Jablonka, Schroeder 1999, Painter et al 2000a, DePaul 2002, Konstantinidou et al 2002, Oh-Park 2002, Koudi et al 2004, van Vilsteren, Greef & Huisman 2004, Kopple et al 2007, Ouzouni et al 2009) the majority have used aerobic exercise interventions.

The aerobic exercise interventions have primarily been conducted before or after dialysis sessions or on non-dialysis (interdialytic) days, using supervised out patient programmes (Goldberg et al 1979, Goldberg et al 1980, Zabetakis et al 1982, Carney et al 1983, Goldberg et al 1983, Hagberg et al 1983, Shalom et al 1984, Harter & Goldberg 1985, Goldberg et al 1986, Carney et al 1987, Ross et al 1989, Akiba et al 1995, Kouidi et al 1997, Kouidi et al 1998, Kouidi et al 2000, Tawney et al 2000, Mercer et al 2002, Molsted et al 2004, Mustata et al 2004, van den Ham et al 2007). However, other studies have favoured supervised aerobic interventions conducted during (intradialytic) dialysis sessions (Painter et al 1986, Moore et al 1993, Frey, Mir & Lucas 1999, Koufaki, Mercer & Naish 2002a & b, Miller et al 2002, Moug et al 2003, Painter et al 2002, Anderson, Boivin & Hatchett 2004, Parsons,

Toffelmire & King-VanVlack 2004, Macdonald et al 2005, Storer et al 2005, Parsons, Toffelmire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008).

The evidence from the exercise studies conducted on interdialytic days, along with evidence from comparative intradialytic versus interdialytic intervention studies, suggests that, interdialytic interventions suffer from a number of problems including poor patient compliance, higher drop out rates and additional costs. The causes of poor patient compliance have included the additional time commitment, difficulties associated with travel to venue and poor levels of health preventing participation (Shalom et al 1984, Konstantinidou et al 2002, Kouidi et al 2004). This has subsequently led to a preference for intradialytic aerobic exercise interventions (Konstantinidou et al 2002, Daul et al 2004, Kouidi et al 2004, Cheema, Smith & Fiatorone-Singh 2005, Johansen 2005, Painter 2008). It is thought that the use of the latter approach enhances patient compliance as it is a more convenient, less burdensome, time efficient approach, which may also encourage older patients and those with significant comorbidities to participate (Konstantinidou et al 2002, Daul et al 2004, Kouidi et al 2004, Painter 2008).

A summary of the identified intradialytic exercise studies is presented in Table 1.3 (Painter et al 1986, Moore et al 1993, Frey, Mir & Lucas 1999, Painter et al 2002, Moug et al 2003, Anderson, Boivin & Hatchett 2004, Parsons, Toffelmire & King-VanVlack 2004, Macdonald et al 2005, Storer et al 2005, Parsons, Toffelmire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008). As two of the originally identified studies included and reported only combined results for PD & HD patients, these studies were excluded (Koufaki, Mercer & Naish 2002a & b).

It can be seen from Table 1.3, that the duration of the intradialytic studies has been typically 3 months or less (Moore et al 1993, Frey, Mir & Lucas 1999, Moug et al 2003, Parsons, Toffelimire & King-VanVlack 2004, Macdonald et al 2005, Storer et al 2005, Toussaint, Polkinghorne & Kerr 2008) or between 3 and 6 months (Painter et al 1986, Miller et al 2002, Painter et al 2002, Anderson, Boivin & Hatchett 2004, Parsons, Toffelimire & King-VanVlack 2006). Therefore, while there is evidence for the relative short term benefits of exercise, there is little evidence on whether continued or sustained improvements are possible beyond these time frames. Furthermore, due to the short duration of these studies there is a lack of data on possible longer term benefits and compliance.

In all but one of the intradialytic studies (Moug et al 2003), the frequency of the intradialytic exercise sessions has been consistent with the number of dialysis sessions per week and have commonly occurred within the first two hours of the dialysis session. All of these studies used cycle ergometers and one study also used a ministepper (Parsons, Toffelmire & King-VanVlack 2006). Four of the intradialytic aerobic studies used an interval type training approach from the outset (Moug et al 2003, Parsons, Toffelimire & King-VanVlack 2004, Macdonald et al 2005, Parsons, Toffelimire & King-VanVlack 2006) and one study incorporated an interval training approach once the prescribed time was achieved (Painter et al 2002).

The intradialytic interventions have generally begun with 2-5 minutes of cycling at a light intensity (<55% HR_{max}) and increased by 1-5 minutes to a total time of 25 minutes (Moug et al 2003), or 30-60 minutes (Painter et al 1986, Moore et al 1993, Frey, Mir & Lucas1999, Miller et al 2002, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005, Parsons, Toffelimire & King-VanVlack et al 2004, Storer et al 2005, Parsons, Toffelimire & King-VanVlack et al 2006, Toussaint, Polkinghorne &

Kerr 2008). It has also been the norm in the majority of studies to include within each exercise session a short warm up and cool down period.

In almost all of the previous intradialytic aerobic exercise studies once the prescribed time was achieved, the intensity of the exercise session was then increased to $\geq$65-70%HR_{max} (Painter et al 1986, Moore et al 1993, Frey, Mir & Lucas1999, Moug et al 2003, Parsons, Toffelimire & King-VanVlack 2004, Macdonald et al 2005). In all but three of the studies, intensities were prescribed and monitored either using percentages of HR_{max} or VO_2max/peak (Painter et al 1986, Moore et al 1993, Frey, Mir & Lucas 1999, Moug et al 2003, Parsons Toffelimire & King-VanVlack 2004, Storer et al 2005) or ratings of perceived exertion (Painter et al 2002, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005). The other three intradialytic studies did not prescribe or monitor intensity, but rather opted for a 'self paced' approach (Miller et al 2002, Parsons Toffelimire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008).

Table 1.3: Summary of intradialytic aerobic exercise interventions

Author (year) country	Number	Age, comorbidity & dialysis vintage	Duration	Exercise protocol	Outcome measures	Significant changes observed
Painter et al 1986, USA Non-randomised controlled	Exercise 14 Control 6	Not reported	6 months	Cycle ergometer Thrice weekly 5 minutes + 2-3 minutes a session up to 30 minutes Initial intensity ~65-70% HR_{max}, progressing to ~75-85% HR_{max}. Individually supervised for first 3 months then general supervision by dialysis staff for next 3 months	VO_2max resting SBP changes in antihypertensives resting heart rate Hct, total cholesterol, HDL	decrease in SBP & increase in VO_2max
Moore et al (1993), USA	Exercise 23 (13M, 10F) -6 week control period	Not reported	3 months	Cycle ergometer Thrice weekly 5-10 minutes + 5-10 minutes a session up to 30 minutes and then workload increased to $\geq$ ~65 -70% HR_{max} Patients encouraged to increase to 60 minutes Option of weekly interval training Individually supervised	VO_2max workrate cardiac output submaximal heart rate, arterial oxygen content rectus femoris biopsy (phosphofructokinase activity, type I/type II muscle fibre area)	increase in workrate, decrease in submaximal heart rate, increase in phosphofructo kinase activity
Frey, Mir & Lucas 1999, USA RCT	Exercise 5 (3F, 2M) Control 6 (3F,3M)	Exercise mean age 40+11years Control mean age 53+13 years Dialysis vintage 66 $\pm$ 93.6 months (Exercise & control) Comorbidity not reported	2 months	Cycle ergometer Thrice weekly Weeks 1-4 -30 minutes with 5 minute warm up and cool down. Resistance gradually increased to ~60-80% HR_{max} Weeks 5-8 exercise session increased to 45 minutes ~ 60-80% HR_{max}	24 hour dietary recall Kt/v prealbumin, transferrin, pre & post diaysis albumin	None

F: female; M: male; %HR_{max}: percentage of maximal heart rate; VO_2max: maximal oxygen uptake; SBP: systolic blood pressure; HDL: high density lipoprotein: Hct:haematocrit;RCT: Randomised controlled trial

Table 1.3 continued

Author (year) country	Number	Age, comorbidity & dialysis vintage	Duration	Exercise protocol	Outcome measures	Significant changes observed
Miller et al (2002), USA Non randomised	Exercise 24 (14F, 10M) Control 32 (18F, 6M)	Exercise mean age 52.8±16 years, dialysis vintage 20.7± 27.5 months Control mean age 56.1± 15.2 years, dialysis vintage 28.7± 25.5 months Low-medium comorbidity	6 months	Cycle ergometer Thrice weekly Patients encouraged to increase time per session by 1-5 mins up to 30 mins and then encouraged to increase resistance as desired General supervision by dialysis staff	Hct, ESA dose, SBP, DBP, antihypertensive medications	decrease in ESA dose, significant increase in Hct
Painter et al (2002), USA RCT	Exercise 10 (5F, 5M) Control 14 (6F, 8M)	Exercise mean age 47.6 ± 11.9 years, dialysis vintage 23.1 ± 24.6 months Control mean age 43.4 + 9.8 years, dialysis vintage 61.8 ± 72.9 months Comorbidity not reported	5 months	Cycle ergometer Thrice weekly Initially 10-15 mins of exercise with no resistance, time increased by 2-3 mins up to 30 mins. Resistance then increased to ~70% $HR_{max.}$ Intervals of 2-3 mins ~80-90% HR_{max} interspersed through out sessions once 20 mins achieved Individually supervised	VO_2peak, domain scores of Short form 36 (SF36)	Increase in VO_2peak Increase in PF score
Moug et al (2003), Scotland, UK Non randomised	Exercise 10 (3F, 7M) Control 6 (2 F, 4M)	Exercise mean age 42.6 ± 12.6 years, dialysis vintage 56.4 months Control 41.0± 8.3 years , dialysis vintage 100.8 months Comorbidity not reported	6 weeks	Cycle ergometer Twice weekly Interval training 5 mins + 5 min break (total 25 mins exercise) increasing to ~75-80% HR_{max} Individually supervised	VO_2max, workrate, Hb, SBP, DBP, anxiety and depression scores, peak eccentric and concentric leg force	Reduction in anxiety levels, increase in workrate

F: female; M: male; $\%HR_{max}$: percentage of maximal heart rate; VO_2max: maximal oxygen uptake;VO_2peak: peak oxygen uptake SBP: systolic blood pressure; DBP:diastolic blood pressure;: Hct:haematocrit; ESA: erythrocyte stimulating agent: Hb: haemoglobin; PF: Physical function; ;RCT: Randomised controlled trial

Table 1.3 continued

Author (year) country	Number	Age, comorbidity & dialysis vintage	Duration	Exercise protocol	Outcome measures	Significant changes observed
Anderson, Boivin & Hatchett (2004), USA	Exercise 19 (15M, 4F)	Mean age 54.7+ 15.6 years Comorbidity & dialysis vintage not reported	6 months	Cycle ergometer Thrice weekly 30-60 minutes per session- initially 5 minutes + 5 minutes up to 30 minutes and then increasing resistance to ~70% HR_{max} Individual supervision for 1st month & monthly review thereafter	VO_2peak Pre/post SBP, DBP, ABP, antihypertensives weight, ECW, Hb, ESA dose	decrease in SBP Trend to lower ESA dose and higher Hct
Parsons, Toffelmire & King-VanVlack (2004), Canada RCT	Exercise 6 (3F, 3M) Control 7 (3F, 4M)	Exercise mean age 60± 17 years, dialysis vintage 35 ± 25 months Control mean age 49 ± 25 years, dialysis vintage 49 + 26 months Low comorbidity	2 months	Cycle ergometer or ministepper Thrice weekly 45 minutes of cycling- 3 x 15 minute bouts within first 3 hours – initially 5minutes + 5 mins up to 30mins & then resistance increased to ~60%HR_{max} Individually supervised	Maximal work capacity Dialysate urea clearance, Kt/v, domain scores of SF36, SBP, DBP, Hb, serum potassium & creatinine,	Increase in dialysate urea removal
Macdonald et al (2005) England, UK	Exercise 9 (7M, 2F) -3 month control period	Mean age 48.4 ± 5.3 years, dialysis vintage 26.7± 5.9 months Comorbidity not reported	3 months	Cycle ergometer Thrice weekly Interval training -2min bout + 2 mins active recovery , 15 bouts per session at 90% HR_{max} for exercise bout & <35% HR_{max} for periods of active recovery Individually supervised	Regional & whole body FM, FFM, ECW & ICW, knee extensor strength, sit to stand, serum & muscle IGF-1 & IGF binding protein-3, SBP, DBP & antihypertensive dose	Decrease in ECW, SBP & antihypertensive medications Increase in sit to stand performance & knee extensor strength

F: female; M: male; %HR_{max}: percentage of maximal heart rate; VO_2peak: peak oxygen uptake; ABP: Ambulatory blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hct: haematocrit; ESA: erythrocyte stimulating agent: Hb: haemoglobin; ECW: extracellular water; FM: fat mass; FFM: fat free mass; ICW: intracellular water; IGF: insulin-like growth factor;RCT: Randomised controlled trial

Table 1.3 continued

Author (year) country	Number	Age, level of comorbidity, dialysis vintage	Duration	Exercise protocol	Outcome measures	Significant changes observed
Storer et al (2005), USA Non randomised	Exercise 12 (5F, 7M) Control 12 (4F, 8M) Healthy volunteers 12	Exercise mean age 44.0± 9 years, dialysis vintage 81.6± 80.2 months Control mean age 39 ± 9 years, dialysis vintage 59.1 ± 83.1 months Low comorbidity	3 months	Cycle ergometer Thrice weekly Initially 20 mins, interval training 4:1 work: rest ratio at 35-55% HR_{max} , then increased to 40mins and load increased further as tolerated Individually supervised	VO_2peak, work rate, leg strength power & fatigability, stair climb, 10m walk time, timed up and go (TUG)	Increase in VO_2peak, work rate, leg strength, fatigability, stair climb performance, decrease in 10m walk time & time taken to complete TUG
Parsons, Toffelmire & King-VanVlack (2006), Canada	Exercise 13 (5F, 8M)	Mean age 53 ± 18 years, dialysis vintage 46± 25 months. Low comorbidity	5 months	Cycle ergometer or ministepper Thrice weekly 60 minutes of cycling- 2 x 30 minute bouts with 30 minutes recovery in between. Selected own intensity Individually supervised	6MWT Kt/v, Urea reduction ratio (URR), SF36 domains scores, Hb, pre dialysis urea	increase in distance covered in 6MWT, increase in Kt/v & URR.
Toussaint, Polkinghorne & Kerr (2008), Australia RCT	Exercise 9 (4F, 5M) Control 10* (6F, 4M) *Cross over at month 4	Exercise median age 67 years (range 60-83) dialysis vintage 35± 31 months Control median age 70 years (range 28-77) dialysis vintage 72 ± 56 months Comorbidity not reported	3 months	Cycle ergometer Thrice weekly Minimum of 30 mins per session Selected own intensity General supervision by dialysis staff	SBP, DBP, PWV, AI, BNP, CRP, Hb, Alb, PTH, Ca x P, homocysteine	Decrease in PWV, BNP

F: female; M: male; $\%HR_{max}$: percentage of maximal heart rate; VO_2peak: peak oxygen uptake SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: haemoglobin; 6MWT: six minute walk test; PWV: pulse wave velocity, AI: augmentation index, BNP: brain-natriuretic peptide; CRP: C- Reactive protein; Ca x P: calcium x phosphate; Alb:albumin

Individual supervision of each exercise session occurred in the majority of the intradialytic interventions (Moore et al 1993, Painter et al 2002, Anderson, Boivin & Hatchett 2004, Storer et al 2005, Macdonald et al 2005, Parsons, Toffelimire & King-VanVlack 2006). Two studies were generally supervised by dialysis staff (Miller et al 2002, Toussaint, Polkinghorne & Kerr 2008) and in one study a switch from individual supervision to general supervision by dialysis unit staff occurred after 3 months (Painter et al 1986). In three studies it was unclear to what extent the exercise programme was supervised (Frey, Mir & Lucas 1999, Miller et al 2002, Parsons, Toffelimire & King-VanVlack 2004).

It has been questioned whether exercise programmes at the intensities used in previous studies are possible, or even necessary, in practice to derive the potential benefits of exercise in the prevalent HD population. It has also been suggested that lower intensity programmes may be of benefit particularly in older populations and those with significant comorbidities (Johansen 2007). However, there is a lack of evidence for the benefits of low intensity exercise interventions, particularly ones which can be broadly applied and potentially be easily incorporated into the routine care of patients (Johansen 2007). Furthermore, it has also been recognised that in reality the onus of maintaining an intradialytic exercise programme would fall primarily on the clinical and dialysis staff of any renal unit (Johansen 2007). It is therefore possible that, in the current financial climate of the National Health Service, complex exercise programmes requiring individual supervision are sufficient to prevent them from becoming part of routine care.

The majority of the intradialytic aerobic exercise studies have used VO_2max/peak as a primary outcome measure (Painter et al 1986, Moore et al 1993, Painter et al

2002, Moug et al 2003, Anderson, Boivin & Hatchett 2004, Storer et al 2005). Moreover, several of these studies have incorporated extensive or stringent exclusion criteria, which suggest much of the prevalent dialysis population, have been excluded (Frey, Mir & Lucas 1999, Moug et al 2003, Macdonald et al 2005).

The patients recruited to these previous studies have generally been younger than the prevalent HD population with an approximate mean age of 49 years. Although there is a lack of information provided on the presence and severity of comorbidities, previous studies appear to have recruited populations with low levels of comorbidity. As such, these studies, along with others, have been criticised for recruiting younger, healthier HD patients (Johansen 2005, Painter 2005, Daul et al 2004). They have also been criticised for the use of limited outcome measures and neglecting the broader clinical impact of changes in VO_2max/peak, such as the potential effect on aspects of physical performance, quality of life, nutritional and clinical status (Cheema & Fiatarone-Singh 2005, Johansen 2005, Painter 2005). This therefore creates difficulties in generalising findings to the wider prevalent HD population.

1.6.1 Changes in physical function as a result of exercise

In intradialytic aerobic exercise interventions where VO_2 max/peak has been used as an outcome measure, either improvements in VO_2 max/peak of approximately 12-22% (Painter et al 1986, Painter et al 2002, Storer et al 2005) or no improvements in VO_2 max/peak have been observed (Moore et al 1993, Anderson, Boivin & Hatchett 2004, Parsons, Toffelimire & King-VanVlack 2004). However, other improvements were shown in these latter studies, such as decreases in systolic blood pressure and increases in submaximal work rates (Moore et al 1993, Anderson, Boivin &

Hatchett 2004), implying that improvements in VO_2 max/peak are not always necessary to derive wider benefits. As a consequence, there is an emerging interest in the potential effects of exercise on other aspects of physical functioning, such as physical performance.

Whilst it would appear from the small number of previous exercise studies using performance tests as outcome measures, that improvements are possible (Cappy, Jablonka & Schroeder 1999, Painter et al 2000, Headley et al 2002, Koufaki, Mercer & Naish 2002a, Koufaki, Mercer & Naish 2002b, Mercer et al 2002, Oh-Park et al 2002, McDonald et al 2005, Parson et al 2006, Cheema et al 2007), only two of these studies have been intradialytic aerobic interventions (Mcdonald et al 2005, Parsons, Toffelimire & King-VanVlack 2006).

Commonly HD exercise studies utilising performance tests have included a walk test such as the six minute walk or North Staffordshire Royal Infirmary (NSRI) walk and gait speed (Cappy, Jablonka, Schroeder 1999, Painter 2000, Headley et al 2002, Mercer et al 2002, Oh-Park et al 2002, Parsons, Toffelimire & King-VanVlack 2006, Cheema et al 2007), with fewer including sit to stand tests (Cappy, Jablonka, Schroeder 1999, Painter 2000, Headley et al 2002, Koufaki, Mercer & Naish 2002a, Koufaki, Mercer & Naish 2002b , Macdonald et al 2005), the timed up and go test (Storer et al 2005) or handgrip dynamometry (Headley et al 2002).

Self reported physical functioning has also recently gained attention and focus in HD exercise studies, but this has been primarily within combined aerobic and resistance or interdialytic aerobic interventions (Painter et al 2000, Oh Park et al 2002, Molsted et al 2004, Ouzoni et al 2009) rather than intradialytic aerobic interventions. These previous studies all reported improvements in PCS alongside improvements in

objective tests. However, not all studies have demonstrated improvements in PCS (Tawney et al 2000, Painter et al 2002, Van Vilsteren, de Greef & Huisman 2004, Parsons 2004, Parsons, Toffelmire & King-VanVlack 2006, Cheema et al 2007) or they have only demonstrated improvements in single domain scores, the most common being the PF or VT domain of the SF36 (Van Vilsteren, de Greef & Huisman 2004, Cheema et al 2007). Those reporting a lack of improvement in PCS have again varied in their intervention using either inter (Tawney et al 2000) or intra dialytic aerobic exercise (Painter et al 2002, Parsons, Toffelimire & King-VanVlack 2004, Parsons, Toffelimire & King-VanVlack 2006) or resistance exercise (Cheema et al 2007) over different periods of time. In the case of the three intradialytic aerobic studies (Painter et al 2002, Parsons, Toffelimire & King-VanVlack 2004, Parsons, Toffelimire & King-VanVlack 2006), it would appear that young and/or high functioning patients with similar or higher self reported functioning compared to population norms were recruited. As such it is possible that the interventions were of insufficient intensity to elicit further improvements.

Based on the evidence to date, it would seem that further studies exploring the effects of intradialytic aerobic exercise on measures of physical performance in the prevalent HD population are required. In addition, because of the limited outcome measures used in many of these previous studies the relationship of such changes with clinical and nutritional status has not been fully explored.

1.6.2 Changes in quality of life as a result of exercise

While improvements in the physical component and/or domains of quality of life are possible as a result of differing exercise interventions, the same does not appear to be so for psychosocial health. The majority of exercise studies to date have reported

no significant improvement in MCS (Painter et al 2000, Painter et al 2002, Van Vilsteren, de Greef & Huisman 2004 , Molsted et al 2004, Parsons, Toffelimire & King-VanVlack 2004, Cheema et al 2007, Ouzoni et al 2009). Only one study has reported a significant change in MCS which was the result of a combined aerobic and resistance exercise intervention (Oh-Park 2002), but, unlike other studies, this study recruited a population with a significantly lower MCS compared with population norms. Although overall the evidence supports the view that changes in MCS as a consequence of exercise interventions are unlikely, improvements in the individual domain scores of mental health such as VT (Van Vilsteren, de Greef & Huisman 2004, Cheema et al 2007) may be possible, but this is largely undetermined and further work is required.

1.6.3 Changes in nutritional status as a result of exercise

Changes in body weight and body composition in HD patients as a result of exercise interventions have been largely over-looked and, as such, the current available evidence is limited. Whilst one study using a resistance exercise intervention has demonstrated that increases in body weight may be possible (Cheema et al 2007), seven other studies (Cappy, Jablonka & Schroeder 1999, Headley et al 2002, Koufaki, Mercer & Naish 2002a, Anderson, Boivin & Hatchett 2004, Van Vilsteren, de Greef & Huisman 2004, Mustata et al 2004, Macdonald et al 2005, Kopple et al 2007) reported no significant change in body weight or BMI. Five of these studies were of only 12 weeks duration (Headley et al 2002, Koufaki, Mercer & Naish 2002a, Van Vilsteren, de Greef & Huisman 2004, Mustata et al 2004, Macdonald et al 2005) and may not have been of sufficient duration to influence body weight. Furthermore, five of the studies utilised either an inter or intradialytic aerobic exercise intervention (Cappy, Jablonka & Schroeder 1999, Koufaki, Mercer & Naish

2002a, Anderson, Boivin & Hatchett 2004, Mustata et al 2004, Macdonald et al 2005) and this type of exercise, regardless of the duration, is not considered to influence body weight in the same manner as resistance training (Evans 2000).

Four later studies (Headley et al 2002, Macdonald et al 2005, Cheema et al 2007, Kopple et al 2007) examined the effects of exercise on FM and FFM stores and three (Headley et al 2002, Kopple et al 2007, Cheema et al 2007) found significant differences in body composition. In the 12 week controlled study of resistance exercise conducted in an older (mean age 62.6 years) group of 49 HD patients, body weight and BMI increased significantly in the intervention group, as did mid thigh circumference and mid arm circumference. Although mid calf circumference also increased in the intervention group, this was not a statistically significant change (Cheema et al 2007). In the smaller uncontrolled study of 10 HD patients (mean age 42.8 years) undertaking resistance exercise, an unexpected significant increase in the sum of seven skinfold measurements was observed, suggesting an overall increase in FM (Headley et al 2002). However, as this was not in keeping with the unchanged weight, the authors questioned the reliability of their measurements and the possibility that changes in ECW had affected the skinfold compressibility. In the small 12 week intradialytic aerobic exercise study of 9 HD patients, again conducted in a younger group (mean age 48.4 years), there was no significant change in body weight, total or regional (leg, arm, trunk) FM or FFM as measured by DXA (Macdonald et al 2005). However, there was a significant decrease in ECW as measured by multifrequency BIA. The authors suggested, this could be due to potential increased losses via sweating. The only other study to investigate changes in body composition was a controlled study designed to examine the effects of three different exercise protocols in the HD population (Kopple et al 2007). This study was a larger study of 51 younger patents (mean age

44 years), over a longer period of 5 months. The results for the three groups combined demonstrated that whilst there was no significant change in body weight or total FM and FFM, regional changes in FM evidenced by significantly reduced tricep skinfold and subscapular skinfold thickness did occur. This study also found that mid calf and thigh muscle area increased, but these increases did not achieve statistical significance.

This small body of evidence suggests that significant changes in body weight, particularly when aerobic protocols are employed are unlikely. However, changes in regional body composition in the absence of changes in body weight may be possible, but may take longer to become apparent when aerobic interventions are used. It would also suggest that further work is needed to examine the effect of exercise interventions on body composition, particularly in older populations.

Very few exercise intervention studies in HD patients have examined changes in dietary intake. It would also appear that no exercise intervention study to date has examined changes in subjective ratings of appetite or possible changes in the composition of energy intakes eg carbohydrate versus fat versus protein. Studies examining changes in dietary intakes have focused on changes in protein intakes using PCR (Cappy, Jablonka & Schroeder 1999, Cheema et al 2007) or changes in energy and protein intakes, using 24 hour recalls (Frey, Mir & Lucas 1999), three day diet diary (Kopple et al 2007) or food frequency questionnaires (Cheema et al 2007). In all of these studies no significant increases in PCR, energy or protein intakes were reported. Two of these studies were of a short 12 week duration (Frey, Mir & Lucas 1999, Cheema et al 2007), one used a resistance training protocol (Cheema et al 2007), and one study used a self paced aerobic protocol before HD (Cappy, Jablonka & Schroeder 1999). Additionally, the intradialytic aerobic study

(Frey, Mir & Lucas 1999) and the study by Cheema et al (2007) could be criticised for using less reliable and less accurate methods of dietary assessment. Therefore, it can be argued that the effects of intradialytic aerobic exercise interventions on appetite and dietary intakes in HD patients are unknown.

1.6.4 Changes in clinical status as a result of exercise

Despite evidence from cross sectional and longitudinal studies in healthy populations indicating that physical activity can decrease CRP levels (Plaisance & Grandjean 2006) and coupled with the knowledge that CRP is a strong predictor of outcome in HD patients (Yeun et al 2000), very few exercise studies have examined or reported the influence of exercise on CRP. To date two studies employing 12 week intradialytic resistance interventions have reported a reduction in CRP (Nindl et al 2004, Cheema et al 2007). One was a small, uncontrolled study (Nindl et al 2004) and whilst reporting reductions in CRP, it was unclear whether they were statistically significant. In contrast to these results, two controlled studies, one intradialytic aerobic intervention of 12 weeks duration (Toussaint, Polkinghorne & Kerr 2008) and one interdialytic combined aerobic/resistance intervention of 5 months, demonstrated no significant change in CRP (Kopple et al 2007). Therefore, whether exercise in HD patients can positively influence CRP requires further study. Furthermore, exploring the impact of exercise on CRP in the wider context would also provide information on whether exercise can positively influence the management of anaemia.

There is some evidence from studies conducted in the pre ESA era that long term (at least 12 months duration) interdialytic high intensity (75-85% HR_{max}) aerobic interventions in young HD patients with little comorbidity can increase haemoglobin

and haematocrit levels over time (Goldberg et al 1983, Goldberg et al 1986). However, the relevance of these findings in a post ESA era where patients are older and with a greater degree of comorbidity is questionable. In the post ESA era, one controlled study (Miller et al 2002) of intradialytic aerobic exercise has suggested positive changes may occur. In this study of intradialytic aerobic exercise a significant reduction in ESA dose and an increased haematocrit were observed at 6 months. Another uncontrolled 6 month study of intradialytic aerobic exercise (Anderson, Boivin & Hatchett 2004) also found that a reduction in ESA dose, coupled with an increased haematocrit occurred as a result of the intervention, but these changes were not statistically significant. CRP was not measured in either study, which would have aided the interpretation of these findings. Conversely, the majority of the available evidence in the post ESA era suggests that neither resistance interventions nor aerobic interventions can positively influence haemoglobin or haematocrit levels (Cappy, Jablonka & Schroeder 1999, Koufaki, Mercer & Naish 2002a, Van Vilsteren, de Greef & Huisman 2004, Mustata et al 2004, Parsons, Toffelmire & King-VanVlack 2004, Parsons, Toffelmire & King-VanVlack 2006, Kopple et al 2007, Toussaint, Polkinghorne & Kerr 2008). However, as haemoglobin levels are being constantly titrated to therapeutic targets (Singh 2008), examining haemoglobin without examining changes in ESA doses could be misleading. In addition as inflammation can affect responsiveness to ESA's, the omission of inflammatory markers such as CRP could be misleading. Only two of the above studies (Kopple et al 2007, Toussaint, Polkinghorne & Kerr 2008) measured CRP levels and only one study examined changes in ESA doses, but they did not report the significance of their findings (Cappy, Jablonka & Schroeder 1999). Due to these omissions in methodology the effect of exercise and, in particular, the effects of longer term interventions on the management of anaemia remain inconclusive.

Further to the changes overleaf, there is a small body of evidence in hypertensive HD patients, that suggests positive improvements in systolic blood pressure (SBP) are possible as a consequence of either combined intradialytic resistance and aerobic interventions (Deligiannis et al 1999, Ouzouni et al 2009), interdialytic aerobic (Hagberg et al 1983) or intradialytic aerobic exercise interventions (Painter et al 1986, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005). However, this evidence is not consistent, with a number of other studies failing to report significant improvements in blood pressure (Shalom et al 1984, Ross et al 1989, Cappy, Jablonka & Schroeder 1999, De Paul et al 2002, Van Vilsteren, de Greef & Huisman 2004, Molsted et al 2004, Parsons, Toffelmire & King-VanVlack 2004, Toussaint, Polkinghorne & Kerr 2008).

Doses of antihypertensive drugs are constantly being titrated to maintain therapeutic blood pressure targets (Mactier 2007); therefore it is possible that decreases in prescribed antihypertensives may occur in the absence of changes in SBP. This aspect however has been ignored in all but two of the studies reporting no significant changes in blood pressure (Shalom et al 1984, Molsted et al 2004). Decreases in antihypertensives have been seen in other studies of either interdialytic (Goldberg et al 1983, Hagberg et al 1983, Goldberg et al 1986) or intradialytic aerobic interventions (Miller et al 2002, Macdonald et al 2005). Changes in interdialytic weight gains and ECW volumes may also influence blood pressure (Lopez-Gomez et al 2005, Charra 2007).These aspects have also been ignored with the exception of one study which reported a significant decrease in ECW which could have contributed to the observed decrease in systolic blood pressure (Macdonald et al 2005).

It is equally possible that, in studies reporting no significant changes in blood pressure, the mode of exercise or the frequency, intensity or duration of the exercise intervention was insufficient to derive such changes. In comparison the majority of studies demonstrating positive effects have been of at least 6 months duration (Goldberg et al 1983, Hagberg et al 1983, Goldberg et al 1986, Painter et al 1986, Deligiannis et al 1999, Miller et al 2002, Anderson, Boivin & Hatchett 2004, Ouzoni et al 2009). Furthermore, the patients recruited to these particular studies were younger with arguably a lower level of comorbidities due to their age and the recruitment process (VO_2max/peak) which may have been influenced the results. Four of the studies demonstrating positive effects were conducted in the pre ESA era (Goldberg et al 1983, Hagberg et al 1983, Goldberg et al 1986, Painter et al 1986) and as it is known that ESAs have a dose dependent effect on blood pressure, potentially aggravating hypertension (van de Borne et al 1992) these studies are perhaps less relevant now. If these studies are excluded then the body of evidence suggesting a beneficial effect of exercise on blood pressure diminishes and is limited to five studies. Two of these studies were combined resistance and aerobic interventions (Deligiannis et al 1999, Ouzoni et al 2009) and three were intradialytic aerobic interventions (Miller et al 2002, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005). This suggests that further work is required to confirm such findings, particularly in older patients and those with a greater degree of comorbidity.

It has been hypothesised that intradialytic aerobic exercise interventions, via what is assumed to be an increase in the perfusion of skeletal muscles, may have the added advantage of increasing solute removal and thereby improving dialysis efficiency and uraemia (Cappy, Jablonka & Schroeder 1999, Kong et al in 1999, Daul et al 2004, Parsons, Toffelmire & King-VanVlack 2006). It is therefore

possible that this affect may act as a contributory mechanism to improvements seen in these types of exercise intervention studies.

One of the first studies to report a possible effect of intradialytic exercise on dialysis adequacy was a study of 11 HD patients, in which, by means of paired dialysis sessions, the effects of a single 60 minute session of intradialytic aerobic exercise versus no exercise was examined (Kong et al 1999). In this study, exercise was shown to significantly reduce the rebound of urea, creatinine and potassium and significantly increase the dialysis efficiency (Kt/v and URR) of that session. A subsequent study, demonstrated by means of two separate studies conducted over a week, that either an extended dialysis time or an unaltered dialysis time plus 30-60 minutes of intradialytic aerobic exercise resulted in improved removal of phosphate, with the latter considered to be more favourable from a patients perspective (Vaithilingham et al 2004).

Two exercise intervention studies, (Cappy, Jablonka & Schroeder 1999, Parsons, Toffelmire & King-VanVlack 2006) have reported improvements in dialysis efficiency attributed to the exercise intervention. Both studies were of a longer duration (12 months and 5 months respectively) with one involving at least 30 minutes of aerobic exercise during dialysis (Parsons, Toffelmire & King-VanVlack 2006) and the other involving 30 minutes of aerobic exercise immediately prior to dialysis (Cappy, Jablonka & Schroeder 1999). In contrast, studies of shorter duration (3 months or less) involving less than 30 minutes of intradialytic aerobic exercise or resistance exercise have failed to show any improvement in URR or Kt/v (Frey, Mir & Lucas 1999, Kopple et al 2007, De Paul et al 2002, Van Vilsteren, de Greef & Huisman 2004, Parsons, Toffelmire & King-VanVlack 2004, Cheema et al 2007). However, none of these studies report having controlled for the factors known to influence

URR and Kt/v such as dialyser size, type, effective blood flow, treatment time and muscle mass. Moreover, whilst it would be reasonable to postulate that the improved efficiency in dialysis could contribute to positive changes in function, nutritional and clinical status, the limited outcome measures used in the above studies make this difficult to confirm.

1.7 SUMMARY AND INTRODUCTION OF THESIS AIMS

The prevalence of individuals on HD is increasing and is predicted to continue to increase. The HD population is also increasing in age and has a higher degree of comorbidity, both of which are likely to result in a greater impairment of physical function, quality of life, nutritional and clinical status causing a consequent increasing burden on NHS resources. Interventions that may simultaneously improve physical functioning, quality of life, nutritional and clinical status of such patients would therefore be of significant value and exercise may be one such intervention capable of this. However, this remains largely undetermined as the majority of studies to date have been short term studies, utilising high levels of intensity and have involved individual supervision by specialist personnel. Moreover, these interventions have primarily focused on changes in exercise capacity and, as such, have been criticised for primarily recruiting high functioning healthy patients. The few studies that have focused on changes in physical performance and quality of life, whilst including a more prevalent HD population, have not examined the relationship of such outcomes with nutritional and clinical status. Therefore, an investigation into whether physical function, quality of life, nutritional and clinical status can be simultaneously improved by a lower intensity, longer term intradialytic exercise intervention with less supervision, and which is inclusive of the prevalent population, is warranted. There is also a distinct lack of evidence in the Scottish HD population and therefore establishing whether such an intervention is beneficial in a population reported to have a higher than average morbidity and mortality is equally warranted. Furthermore, it is apparent that due to the complexity of CKD, a study design that incorporates multiple outcome measures beyond those included in previous studies, is justified to provide a better understanding and interpretation of any potential findings.

The primary aims of the thesis are therefore:

1. To investigate the effect of a 12 month low to moderate intensity intradialytic exercise intervention on function, quality of life, nutritional status and clinical status in long term HD patients.

2. To explore associations between functional indices with quality of life, nutritional status and clinical status over a 12 month low to moderate intensity intradialytic exercise intervention.

CHAPTER 2: METHODS

2.1 SUBJECTS, ETHICAL APPROVAL AND RECRUITMENT

Ethical approval was obtained from Queen Margaret University (QMU) and Fife Local Research Ethics Committee (reference number 950). Recruitment began in February 2003 and ran for 12 months. The study was completed in February 2005.

Patients, who dialysed within NHS Fife, were eligible to volunteer. Patients were invited to volunteer via posters placed at various locations throughout the renal unit. Notes of interest were registered with the Unit Charge Nurse and followed up by the Investigator. Interested patients were provided with an information sheet and given the opportunity to ask questions prior to obtaining informed written consent and the physician screen.

The inclusion criteria were as follows: On maintenance haemodialysis for at least 6 months and younger than 80 years of age.

The exclusion criteria were as follows: Acute or chronic medical conditions that could make an exercise intervention hazardous (recent myocardial infarction, leg shunt, unstable ischaemic heart disease); or bias the outcome measures (neoplastic disease) or makes the outcomes difficult to assess (cerebrovascular disease, leg amputation).

Given that there is published data on the benefits of exercise in HD *per se*, including a control (ie non-exercising) group could be considered controversial and contrary to

the Declaration of Helsinki (Shephard 2002). Whilst a solution to this could have been to allow any control group an opportunity to undertake the exercise programme after the 12 month period this was not feasible due to a lack of resources. Therefore the following approach was adopted: Firstly patients served as their own controls. This was done by means of a one month run in period prior to the commencement of the 12 month intervention and has used in other CKD exercise studies (Moore et al 1993, Nindl et al 2004). Secondly, a number of patients who would have been eligible to participate, but who did not want to exercise were approached to serve as a non-randomised control group. These patients were informed that should they subsequently wish to participate in exercise during the 12 month recruitment period they could do so.

2.2: EXPERIMENTAL PROTOCOL

The experimental protocol is represented schematically in Figure 2.1. Initially patients underwent a physician screen to confirm eligibility for participation. Once eligibility was confirmed a comorbidity risk score was assigned by the physician (Khan et al 1993) (Table 2.1) and the patients' date of birth, dialysis vintage (length on time on dialysis in months) were recorded.

The patient's diagnosis of CKD was obtained from the unit's electronic record system (Proton, Clinical Computing plc). Diagnoses were then grouped into five categories glomerulonephritis, interstitial nephritis, diabetic nephropathy, multi-system disorders and unknown diagnosis as per the Scottish Renal Registry (SRR) approach.

Table 2.1: **Comorbidity risk score** (Khan et al 1993)

Risk (score)	Criteria
Low (1)	Age < 70 years and no comorbid illness
Medium (2)	Age 70-80 years OR Age < 80 years with one of the following: Angina, previous myocardial infarction, cardiac failure, chronic obstructive airways disease, pulmonary fibrosis, liver disease OR Age < 70 years with diabetes mellitus
High (3)	Age > 80 years OR Any age with two or more organ dysfunctions in addition to end stage renal failure OR Any age with diabetes and cardiopulmonary disease OR Any age with visceral malignancy.

The outcome measures (functional, quality of life, nutritional, clinical) were made at -1 month, 0 months, 3, 6, 9 and 12 months and was guided by previous exercise studies identifying 3 monthly time points as the norm. At each time point the measurements coincided with the first monthly mid week dialysis session (either Wednesday or Thursday depending on dialysis days).

The timing of the measurements also coincided with the dialysis unit's own policy and those of NHS Quality Improvement Scotland (CSBS 2002) and UK Renal Association guidelines (Mactier 2007) for the measurement of biochemical and dialysis adequacy parameters.

All measurements were conducted within or close to the dialysis unit. This approach was utilised to minimise any perceived burden to patients that could act as a potential barrier to participation (Cheema et al 2006) and to reduce additional costs through changes to patient-hospital transport arrangements.

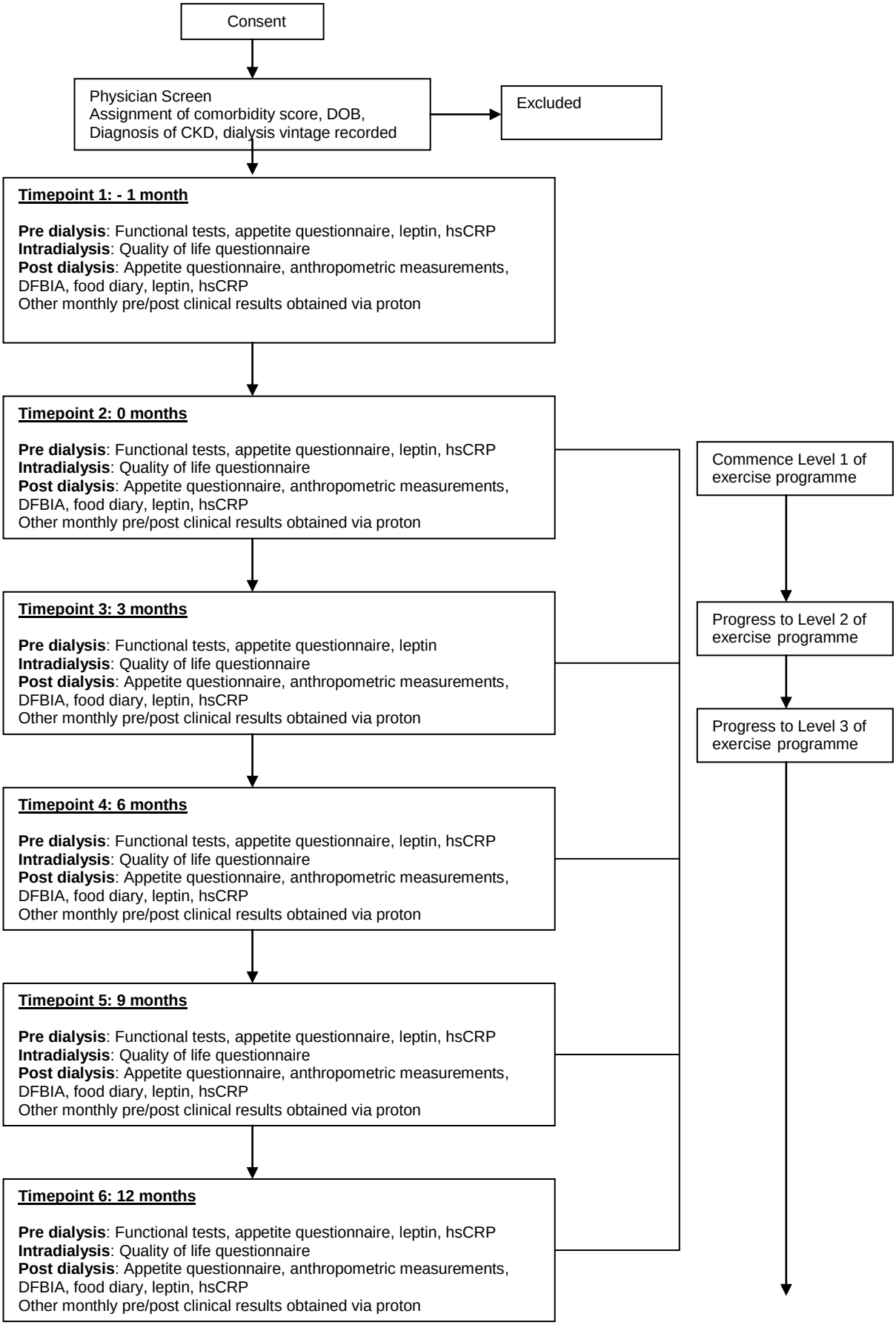
The measurements of functional ability (sit to stand, timed up and go and handgrip test) were completed immediately before the dialysis session.

On commencement of the dialysis session a blood sample for high sensitivity C-reactive protein (hsCRP) and leptin analysis was obtained. Following this patients were given the appetite visual analogue score (VAS) and the quality of life questionnaire to complete.

On discontinuation of the dialysis session another appetite VAS was given and another blood sample for hsCRP and leptin analysis was obtained. Immediately post dialysis the measurements of nutritional status and body composition were obtained (height (at recruitment only), weight, limb circumferences, skinfolds and dual frequency bioelectrical impedance analysis (DFBIA)). Patients were given a food diary to be completed and returned at the next dialysis session.

All other pre and post dialysis results (eg serum potassium, serum albumin etc) and clinical information (eg pre dialysis blood pressure, changes in medications) were obtained via the dialysis units' electronic patient record system. In addition dialysis adequacy results for the relevant time points were obtained via the dialysis unit's urea kinetic modelling programme.

Figure 2.1: Schematic experimental protocol



2.3 FUNCTIONAL PERFORMANCE

As the selected functional outcome measures were all submaximal measurements of performance, they were completed immediately prior to the dialysis session. This approach has previously been utilised in the HD population (Cheema et al 2006).

2.3.1 Sit to stand 60 second test

The equipment used for this test and standardised throughout was a stopwatch and a straight back chair with no arms. The seat was of standard height (46cm) as used in other studies (Ozakevli et al 2007). The chair was placed against a wall (in the clinic room next to the unit) to stop the chair from moving. The patient sat in the middle of the chair with back straight, feet flat on the floor, arms crossed at the wrists and held against the chest.

Before starting the test, patients were told that they should squat over and touch the chair in the sitting phase and to fully extend their knees in the standing phase (Koufaki & Mercer 2006). Patients were told that should they feel unwell or unable to continue that the test would be discontinued. The test was demonstrated to patients prior to commencement. On the verbal signal of ‘’go’’ the patient rose to a full stand, and then returned to a seated position. The patient repeated this movement as many times as possible within the 60 second period. One trial was administered and the total number of complete repetitions in 60 seconds was recorded (Dinan & Skelton 2003).

2.3.2 Timed up and go test

The equipment used for the three metre timed up and do (TUG) test was a stopwatch, a standard straight backed chair with no arms (seat height 46cm), a tape measure and a cone (Podsiadlo & Richardson 1991). Patients wore their usual footwear and no physical assistance was given.

The chair was placed against a wall in a clear, unobstructed section of corridor in the renal unit. The chair faced the cone marker which was positioned exactly 3 metres away (measured from the back of the cone to a point on the floor level with the front edge of the chair). The patient sat in the middle of the chair with their feet flat on the floor and hands on their thighs. On the verbal signal of ‘’go’’ the patient pushed off and walked (but did not run) as quickly as possible (comfortable, fast and secure pace) around the cone, then walked back and sat down. One practice test and one trial test was conducted and the time to the nearest one-tenth of a second was recorded (Dinan & Skelton 2003).

2.3.3 Handgrip strength

Handgrip strength was measured using an analogue dynanometer (Grip-A 5001, Takei scientific instruments Co. Ltd) with a measuring range 0-100kg. The grip range was adjusted for each patient until the second joint of forefinger was bent through 90^{o}. The non-dominant arm was used unless precluded by the presence of an arteriovenous fistula. It is recommended that the arm for the arteriovenous fistula should not be used for strength assessment as a precautionary measure to avoid damaging the fistula (Koufaki & Mercer 2006). The baseline measurement position was noted to standardise subsequent measurements for individual patients.

Measurements were made with subjects standing with their arm hanging by their side or where mobility precluded this, measurements were taken with subjects sitting on a chair with no arms, arm hanging by their side. One measurement was taken and recorded to the nearest 1kg (Bohannon & Schaubert 2005).

For comparative purposes the results of the functional tests at recruitment were contrasted with available normative data. However it would appear that available normative data for the 60 second version of the sit to stand test is limited; therefore in the absence of any other identified norms, Australian data compiled by Ritchie et al (2005) on adults aged 55-70 years (mean age 62.6 years) was used. Normative data for healthy adults aged 60 -69 years derived from a meta- analysis of primarily American studies was used for the time taken to complete the timed up and go test , again in the absence of any other identified data (Bohannon 2006). The results for handgrip strength were compared to normative data for healthy UK adults, with a mean age of 53 years (Kuh et al 2005)

2.4 QUALITY OF LIFE

The standard 4-week recall short form-36® version 2 (SF-36v2) questionnaire was used to measure perceived quality of life. Permission to use and reproduce the English version of the SF-36v2 was obtained from qualitymetric.com.

The self administered questionnaire was given and completed at the beginning of the dialysis session (within the first 30 minutes) at each time point. For those with impaired sight the questionnaire was read to the patient verbatim by a member of dialysis staff to minimise bias. The questions addressed a patients' ability to perform vigorous activity, activities of daily living and participation in social, family and

occupational activity. The questions also addressed the patients' mood, their current and past health, energy levels and susceptibility to illness.

Questionnaires were then scored via the online programme at qualitymetric.com. Scales are scored on a 0 to 100 possible range and normalised to general population means of 50, with a standard deviation of 10, thus allowing comparison of summary component results and domain results with a general population norm based score of 50. Scores were recorded for the two summary components PCS, MCS and the eight domains (Table 2.2). The domain scores influence both summary scores, but with different weightings. PF, RP, BP, GH domain scores significantly influence the PCS and VT, SF, RE, MH domain scores significantly influence the MCS (Ware et al 2007).

Table 2.2: Interpretation of SF-36 domain scores (Ware et al 2007)

Scale	Lowest possible = 0(floor)	Highest possible = 100(ceiling)
Physical Functioning (PF)	Very limited in performing all physical activities, including bathing or dressing, because of health	Performs all types of physical activities, including the most vigorous, without limitations caused by health
Role-Physical (RP)	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Bodily pain (BP)	Very severe and extremely limiting pain	No pain or limitations caused by pain
General Health (GH)	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Social Functioning (SF)	Extreme and frequent interference with normal social activities because of physical or emotional problems	Performs normal social activities without interference caused by physical or emotional problems
Role-emotional (RE)	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Mental Health (MH)	Feeling nervousness and depression all of the time	Feels peaceful, happy and calm all of the time
Vitality (VT)	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Physical Component Summary (PCS)	The lowest level of physical scales scores, health generally rated ‘’poor’’	The highest level of the physical scale scores, health generally rated ‘’excellent’’
Mental Component Summary (MCS)	The lowest level of mental, social and emotional scales, health generally rated ‘’poor’’	The highest level of mental, social and emotional scales, health generally rated ‘’excellent’’

2.5 NUTRITIONAL STATUS

As highlighted in chapter 1 (section 1.4.1) there is no definitive single method available to assess nutritional status (Sundell et al 2007), therefore this study utilised, a number of methods concomitantly which are detailed below. In addition, prior to the commencement of the exercise intervention, work was undertaken to validate the nutritional outcome measures used within this population and this is reported in Chapter 3.

All nutritional measurements were made post dialysis, with a view to minimising any effect of alterations in total body water and to allow the standardisation of subsequent measurements. Standard clinical procedures were followed with respect to health and safety for hand washing and cleaning of equipment.

2.5.1 Height

As the population were adults, stature was measured at the point of recruitment to the study only. Stature was measured using a fixed wall stadiometer (range 60-220cm) with an accuracy of 0.1cm.

The method required patients to stand with the feet together and the heels, and with the buttocks and upper part of the back touching the stadiometer scale. The head was placed in the frankfort plane prior to measurements being taken. The frankfort plane was achieved by lowering the edge of the eye socket into the same horizontal plane as the tragion (the notch superior to the tragus of the ear) ensuring that when aligned the vertex is the highest point of the skull (Norton & Olds 1996).

2.5.2 Weight and body mass index

Weight was measured to provide a general description of body size and total mass (Fat Free Mass + Fat Mass). Coupled with stature its measurement was also used to calculated body mass index (BMI =Kg/m^2) at each time point. Furthermore, as changes in interdialytic weight gain are thought to influence pre dialysis blood pressure (Lopez-Gomez et al 2005, Charra 2007), interdialytic weight gain was also recorded at each time point.

In haemodialysis patients body weight is commonly influenced by changes in total body water (TBW). It is therefore routine practice to monitor 'dry oedema free' weight. A 'dry oedema free' weight is a weight that is considered to be the lowest weight an individual receiving dialysis can tolerate without the symptoms of low blood pressure (Jaegar et al 1999). The post dialysis weight is considered to reflect this. Patients were therefore weighed post dialysis at each time point in light indoor clothing with their shoes removed. Weight was measured to the nearest 0.1Kg using electronic Secca sit on scales with an accuracy of 0.01Kg. Calibration of these scales was regularly performed by the hospital physics department.

2.5.3 Limb circumferences and skinfold thicknesses

Protocols published by the International Society for the Advancement of Kinathropometry (ISAK) were used where relevant (Norton & Olds 1996). All measurements were undertaken by the author, who is a trained level 3 ISAK Accredited (Instructor) anthropometrist. The authors' known technical error of measurement (TEM) for skinfolds and circumferences were derived prior to the commencement of the study. From these repeated measures of 20 subjects TEM's

are as follows: mid arm circumference =0.05cm (0.2%), tricep skinfold =0.1mm (0.74%), calf circumference =0.07cm (0.19%) and calf skinfold =0.11mm (0.93%). The intraclass correlation coefficient (ICC) for these measurements was 1.0.

Midarm and calf circumferences were measured using a flexible steel tape measure (Lufkin W606PM). Tricep and calf skinfold thickness was measured to 0.2mm using Harpenden skinfold calipers. The Harpenden calipers were calibrated by Harpenden prior to commencing the study.

Anthropometric measurements were standardised to the right side of the body (Norton & Olds 1996) unless the presence of a fistula precluded this. Comparisons between the left and right sides of the body have shown that there is either no significant difference in skinfold thickness (Wormsley & Durnin 1973) or that the differences, although statistically significant, are of no practical significance (Martorell et al 1988). However, where any deviations or variations were made, these were noted to allow for the standardisation of subsequent measurements.

For comparative purposes, at recruitment, anthropometric data was contrasted to reference data of healthy individuals aged 50-59 years collected as part of the US National Health and Nutritional Examination Survey (NHANES) collected 1999-2002 (McDowell 2005). Whilst it is currently common practice in the UK to compare anthropometric results with previous US NHANES data collected 1971-1974 (Bishop et al 1981) this data does not include norms for calf circumference and given the secular increase in BMI this earlier data was not considered applicable.

2.5.3.1 Mid arm circumference

Mid arm circumference (MAC) is considered to indirectly estimate fat and fat free mass. In combination with the tricep skinfold measurement it also allows the calculation of mid arm muscle circumference.

The point of measurement for MAC is the midpoint equidistant from the acromiale and radiale. Patients were asked to assume a relaxed position, arms hanging by their sides and with their shoulder girdle in a mid position in order to allow identification of the acromiale and radiale.

The acromiale is the point at the superior and external border of the acromion process of the scapula. This was located by the Investigator positioning themselves behind the right side of the patient. The Investigator palpated along the spine of the scapula to the corner of the acromion. The straight edge of a pencil was then applied to the lateral external border of the scapula to identify the most lateral part of the border of the acromion process. The most superior, lateral margin was located with the side of the thumb and marked with a hypoallergenic pencil.

The radiale is the point at the proximal and lateral border of the head of the radius. This was located by the investigator again being positioned at the right side of the patient. The right thumb was used to palpate downward in the lower portion of the lateral dimple of the right elbow. If necessary, patients were asked to pronate or supinate their forearm to produce a rotary movement of the head of the radius. The position was then marked with a hypoallergenic pencil.

Once identified the linear distance was measured between the acromiale and radiale landmarks with the arm relaxed and extended at the side, avoiding any curvature surface of the arm. A horizontal mark using a hypoallergenic pencil was placed at the level of the midpoint between these two landmarks. The mark was then projected around to the posterior surface of the arm as a horizontal line (to allow the measurement of the tricep skinfold)

In order to obtain the MAC itself, patients continued to assume a relaxed position with arms hanging by their sides. The patient's arm was abducted slightly to allow the steel tape measure to be passed around the arm. The tape was placed perpendicular to the long axis of the arm when the subject was standing erect .The circumference was measured at the marked level of the mid-acromiale radiale. Where necessary the above measurement was undertaken with patients in the sitting position, using a standard chair with no arms and a low back, but otherwise following the above protocol.

2.5.3.2 Tricep skinfold thickness

The tricep skinfold site is the most widely used single skinfold site for making an estimate of total fat mass stores operating on the assumption that subcutaneous fat stores at this point are representative of whole body fat stores (Brodie & Hutcheon 1998) However, in this study it was used to examine regional changes only.

The patient was asked to assume a relaxed position with the left arm hanging by the side. The right arm was also relaxed, but this time with the shoulder joint slightly externally rotated and the elbow extended at the side of the body.

The skinfold was raised parallel to the long axis of the arm at the site of the posterior mid-acromiale radiale landmark. The skinfold was grasped and lifted (raised) at the marked line so that a double fold of skin plus the underlying subcutaneous adipose tissue was held between the thumb and index finger of the left hand. The nearest edge of the contact faces of the caliper were applied 1 cm away from the edge of the thumb and finger. The measurement was recorded two seconds after the full pressure of the caliper was applied (Kramer & Ulmer 1981). This approach was used as adipose tissue is compressible and a constant recording time enables test/retest comparisons to be made while controlling for the known compressibility (Martin et al 1985). Two measurements were taken and the mean value recorded.

2.5.3.3 Mid arm muscle circumference

Mid arm muscle circumference (MAMC) is considered to be an estimate of fat free mass. It represents the circumference of the inner circle of muscle mass surrounding a small central core of bone (Gurney & Jelliffe 1973) and is derived from the measurements of MAC and TSF as follows:

$$MAMC\ (cm) = (MAC\ (cm) - (\pi \times TSF\ (mm)).$$

It should be noted that the equation does not take into account inter-subject variation in the diameter of the humerus relative to the MAMC (Frisancho 1981). Whilst this method is commonly used to reflect whole body FFM stores, in this study it was used to examine regional changes in FFM only.

2.5.3.4 Calf circumference

Calf circumference (CC) is an estimate of FFM and FM and as such is similar to MAC. In combination with calf skinfold measurement it allows the calculation of calf muscle circumference.

Patients were in a sitting position with feet separated. The right leg was positioned at a 90^{o} angle. The measurement was taken at the most medial aspect of the calf at the level of the maximal girth. The maximal girth was determined by using the middle fingers to manipulate the position of the steel tape in a series of up or down measurements to determine the maximum girth and marked with a small horizontal line on the medial aspect of the calf.

2.5.3.5: Calf skinfold thickness

Calf skinfold (CSF) is an estimate of FM and similar to TSF. The patient was asked to assume the same position used for the measurement of calf circumference. The calf skinfold, parallel to the long axis of the leg, was measured at the point of the maximal circumference on the most medial aspect of the calf as above.

The skinfold was grasped and lifted (raised) at the marked line so that a double fold of skin plus the underlying subcutaneous adipose tissue was held between the thumb and index finger of the left hand. The nearest edge of the contact faces of the caliper were applied 1 cm away from the edge of the thumb and finger. The measurement was recorded two seconds after the full pressure of the caliper was applied (Kramer & Ulmer 1981). Two measurements were taken and the mean value recorded. Like TSF it was used to examine regional changes.

2.5.3.6: Calf muscle circumference

Calf muscle circumference (CMC) is considered to be an estimate of FFM (similar to MAMC) and is derived from CC and CSF measurements above as follows:

$$CMC\ (cm) = (CC\ (cm) - (\pi \times CSF\ (mm))$$

The above equation does not take account of inter-subject variation in the diameters of the tibia and fibula relative to the CMC. CMC was used to examine regional changes in FFM.

2.5.4 Bioelectrical impedance analysis

Dual frequency bioelectrical impedance analysis (DFBIA) was used to examine changes in whole body composition versus regional changes. The machine used (DualScan 2005, Bodystat UK) operated at the fixed previously defined optimal frequencies of 5 kHz and 200 kHz (Hannan et al 1995)

DFBIA measurements were taken 15 minutes post dialysis (Di Iorio et al 2004) and were conducted in an ambient environment of 22^{o}C (Kyle et al 2004), following accepted and standard methodologies. Use of the unit's examination couch allowed patients to lie in the supine position, arms and legs apart. Two electrodes (>4cm^{2}) were placed on both the right hand and foot or on the side contralateral to the arteriovenous fistula where necessary (Woodrow et al 1997).

The regression equations developed by Hannan et al (1995) at the fixed frequencies of 5 kHz and 200 kHz were then used to estimate extracellular water (ECW) (L) and

total body water (TBW) (L) respectively. Although these regression equations were not developed in a dialysis population, in the absence of other validated regression equations at the fixed frequencies of 5 kHz & 200 kHz, these equations were deemed to be appropriate. This was because of the similarities between the present study population with the original study population and because it was postulated that the pattern of any changes in TBW (eg expansion of ECW) in the original study group would be similar to that seen in this population.

The equations used were as follows:

ECW (L) = 0.1782 (Ht (m^2)) / R5 + 0.0688 x wt (kg) + 3.771

TBW (L) = 0.2391 (Ht (m^2)) / R200 + 0.1889 x wt (kg) + 2.971 x Gender (female = 0, male = +1) + 5.4641.

Where: ECW = extracellular water; TBW = total body water; Ht= height; Wt = weight; R5= resistance measurement at 5 kHz; R200 = resistance measurement at 200 kHz.

Whilst it is recognised that HD patients may violate the assumption that 73.2% of TBW is FFM, in the absence of any other known equations, FFM, FM and ICW were then derived from ECW and TBW as follows:

Total body FFM (kg) = TBW/0.732;

Total body FM = Weight (kg) - FFM (Kg);

*ICW = TBW-ECW;

ECW: *ICW ratio

ECW: TBW ratio

Where: *ICW = Intracellular water

Total FM and FFM, TBW and ECW were also expressed as percentages of body weight.

Normative data for total FM and FFM derived from DFBIA appears to be lacking. Therefore for comparative purposes, results at recruitment were contrasted to available age matched normative data for healthy Europeans of similar BMI's aged 55-64 years, derived using single frequency BIA (Kyle et al 2000).

2.5.5 Interdialytic food diary

In order to determine the effects of exercise on short term dietary intakes, patients were issued with a food diary and asked to record the time and consumption of all food and beverages during the interdialytic period (commenced immediately following the midweek dialysis session and discontinued at the commencement of the next dialysis session). Clear verbal and written instructions were given to all patients for completion of the food diary. Patients were instructed to provide detailed descriptions of all foods and beverages including brand names were relevant, along with the method of preparation and cooking. They were also instructed patients to estimate food portions by using standard household measures and examples were given. Food diaries were then checked with individual patients on return and where required portion sizes were clarified using the Ministry of Agriculture Fisheries and Food photographic atlas of food portion sizes in order to further minimise errors associated with difficulties in accurately quantifying portion sizes .

The food diaries were analysed using a dietary computer analysis programme, WinDiets Research (Univation Ltd 2005). Due to the short duration of the food diaries only estimates of total energy (Kcal) intake, carbohydrate (g), fat (g) and protein (g) intakes were obtained.

2.5.6 Protein catabolic rate derived from urea kinetic modelling

By virtue of stage 5 CKD, haemodialysis patients cannot excrete significant amounts of urinary nitrogen. Therefore, the rate of increase in serum urea levels between two subsequent dialysis sessions is considered a reliable function of dietary protein (nitrogen) intake, provided there is no negative or positive nitrogen balance as seen in catabolic or anabolic state. Under such circumstances PCR is likely to overestimate protein intake (catabolic state) or conversely underestimate protein intake (anabolic state) (Shinaberger et al 2006).

This indirect measure of protein intake is referred to protein catabolic rate (PCR). PCR was obtained via the formal urea kinetic modelling programme which is used on a monthly basis within the unit and was, therefore, conveniently available at all time points. The PCR was normalised for ideal body weight (BMI =23kg/m^2), as it can be misleading in people who are over or under nourished or where weight changes occur over time.

2.5.7 Appetite visual analogue scales

Visual analogue scales (VAS) were used to examine the possible impact of exercise on patients' subjective sensations of hunger, satiety, fullness and prospective consumption (desire). As highlighted in Chapter 1, VAS are now a well established method for measuring variables of appetite and have previously been used in the CKD population (Wright et al 2001, Wright et al 2003, Zabel et al 2009a). They consist of a question followed by a horizontal line (100mm long) with a description at each end ranging from 'I am not hungry at all' to 'I am the hungriest I have ever

been' and provide a continuous scale of measurement , thought to be sensitive to small changes (Stubbs et al 2000).

Patients were presented with the four VAS immediately pre and post dialysis and given clear instructions on how to complete at each time point. After explanation of the four variables of appetite, patients were asked to place a vertical line through the horizontal line that best represented how they were feeling in relation to the four variables at that particular moment in time. Individual scores were determined by measuring the distance along the 100m horizontal line from the left side of the line to the mark made by the individual patient.

2.6 CLINICAL STATUS

As highlighted in Chapter 1 (see section 1.2.4 and 1.6.4) previous exercise studies have generally included limited and differing clinical outcome measures. Therefore in a bid to extend previous work and in view of the all multifactorial, complex inter-relationships that exist in CKD, outcome measures that had been highlighted in previous studies as being potentially relevant in the context of exercise interventions were included.

2.6.1 Urea reduction ratio

Urea is the bulk catabolite of protein and constitutes the great majority of waste nitrogen accumulated between dialysis sessions. It is a low molecular weight solute with unchanged chemical structure; which is easily measured in blood. Its distribution volume corresponds approximately to the volume of total body water. Urea kinetics during haemodialysis has been definitely substantiated and as it is

readily dialysed, it is a widely used for the measurement of dialysis efficiency (European Renal Best Practice Guidelines 2002).

The Urea Reduction Ratio (URR) is calculated from the pre dialysis and post dialysis serum urea levels to yield a percentage and indication of dialysis adequacy as follows:

URR= 100 x (1 – [urea post] / [urea pre]).

URR results at recruitment were compared to the UK Renal Association target of URR of >65% (Mactier 2007).

2.6.2 Urea kinetic modelling: eKt/V

Kt/V is a dimensionless number that quantifies dialysis adequacy and is considered to be a more sophisticated than URR (Hoenich & Pearce 2003). The term Kt/V describes the fractional clearance of urea during a dialysis session where:

K= the urea clearance during dialysis (dependent on urea clearance of dialyser and blood flow rate),

t = the treatment duration

V = the urea distribution volume within the body (related to FFM)

Dual pool or equilibrated UKM (eKt/V) considers urea to be distributed in two pools within the body, the intracellular fluid (ICF) and the extracellular fluid (ECF). During dialysis, changes in the urea concentration of ICF lag behind those in the ECF and, following the end of dialysis, a ‘rebound’ in the serum level of urea occurs. This is due to the diffusion of urea from the ICF to the ECF until equilibrium occurs

(approximately 30-60 minutes post dialysis) and, as such, the predictive formula for the calculation of eKt/V corrects for this (Kooman, van der Sande & Leunissen 2001) The eKt/V was obtained from the dialysis units existing urea kinetics software package (Pinnacle- The complete urea kinetics software package version 1.2, manufacturer Fresenius). This package was also used to obtain information on the other factors that influence the calculation of eKt/V, namely prescribed and effective (achieved) blood flow rate, dialysate flow rate, duration of dialysis session and dialyser type. eKt/V results at recruitment were compared to the UK Renal Association target of eKt/V >1.2 (Mactier 2007).

2.6.3 Biochemistry

The relevant biochemical results were recorded from the coinciding routine monthly bloods taken at the midweek dialysis session for each patient. These were obtained from the electronic patient record system (Proton). These bloods are taken in accordance with Scottish Renal Registry/Renal Association protocols and analysed in the hospital's own accredited laboratory.

The results recorded were; pre and post dialysis serum sodium, urea, bicarbonate, potassium, creatinine. Pre dialysis serum phosphate, corrected calcium, albumin, haematocrit and haemoglobin. Where relevant, results at recruitment were compared with Fife NHS Area Laboratories reference values or the UK Renal Association therapeutic targets for HD patients (Mactier 2007).

2.6.4 High sensitivity C-reactive protein

The measurement of pre and post dialysis high sensitivity C-reactive protein (hsCRP) was taken to examine the possible effects of exercise on the generation of hsCRP and to examine possible changes in hsCRP over time. Results were obtained via the routine monthly blood samples and analysed by the hospital's own accredited laboratory. Results at recruitment were compared with the Fife NHS Area Laboratories reference value for hsCRP (normal <5mg/l).

2.6.5 Leptin

In addition to the routine blood samples, a further pre and post blood sample (5 mls) was taken at each time point. This was to ascertain pre and post leptin values. Pre and post samples were taken with a view to exploring possible acute effects of exercise on leptin levels and to examine the possible effects of exercise on leptin levels over time.

These samples were labelled separately and were sent to the hospital laboratory by dialysis staff for spinning and storage at -80^{o}C. The samples were then collected from the laboratory every 3 months by the author and transported to Queen Margaret University (cold storage transport). At Queen Margaret University they were again stored at -80 ^{o}C until analysis by the author.

Leptin Elisa (DRG International, Inc)

All reagents and samples were allowed to come to room temperature before use and all reagents were mixed without foaming. Grossly haemolysed specimens were

discarded before proceeding. Once the test was started all steps were completed without interruption.

New disposable plastic pipette tips were used for each reagent, standard or specimen in order to avoid cross contamination. For the dispensing of the substrate solution and the stop solution pipettes with non-metallic parts were used as per manufacturer's instructions.

Standards and samples were pipetted onto the bottom of the well. For pipetting the leptin conjugate and stop solution the pipette was held in a vertical position above the well and the correspondent solution was dispensed into the centre of the well so that a complete mixing of leptin antibody with the sample or standard and of the stop solution with the substrate solution was achieved.

All reagents were prepared prior to starting the assay to ensure an equal time elapsed for each pipetting step without interruption. Direct sunlight was avoided on the microtiter plate during incubation with the substrate solution as per manufacturer's instructions. Samples were diluted 1:5 with assay buffer prior to testing.

Assay Procedure (DRG International, Inc)

100µl of diluted leptin conjugate was dispensed into each coated microtiterwells and the plate was then incubated for 1 hour at room temperature. The content of the wells was then briskly shaken out and rinsed 3 times with diluted wash solution, 300µl per well. Then 50µl of standards, controls and diluted samples were dispensed into the appropriate wells. in order to run the controls and samples in dual 50µl of leptin antiserum was then dispensed into each well in the same order as the

standards and the samples, ensuring that the pipette was held vertically above the well to dispense the antiserum into the centre of well to ensure that complete mixing of the antiserum with the standard or sample was achieved. The plate was then incubated overnight at $4^{o}C$ in a humidity chamber.

After 24 hours the content of the wells were briskly shaken out and rinsed 3 times with diluted wash solution, 300µl per well, with the wells being struck on absorbance paper to remove residual droplets. Next 100µl of the diluted second antibody was dispensed into each well after which the plate was then incubated for 1.5 hours at room temperature. The content of the wells were again briskly shaken out and rinsed 3 times with diluted wash solution, 300µl per well. Next a 100µl of enzyme complex was dispensed into each well, with the plate then being incubated for 45 minutes at room temperature. The content of the wells were again briskly shaken out and rinsed 3 times with diluted wash solution, 300µl per well before being struck on absorbance paper to remove residual droplets again. Finally a 100 µl of substrate solution was added at timed intervals prior to the plate being incubated for 20 minutes at room temperature. The enzymatic reaction was stopped by adding 50 µl of stop solution to each well at timed intervals.

Wells were read within 10 minutes using a micro well reader capable of determining absorbance at 450 $\pm$ 10nm. A standard curve was constructed by plotting the average absorbance (Y) of each reference standard against the corresponding concentration (X) in ng/ml to determine results. The lowest detectable value of leptin that could be distinguished from the zero standard was 0.2µg/ml.

2.6.6 Blood pressure

Pre dialysis systolic and diastolic blood pressure measurements for the relevant time points were obtained via the electronic patient database (proton). These measurements were taken by dialysis staff (using a Crikiton Dinamap ^{TM} Plus) from the non-arteriovenous fistula arm (minimises risk of erroneous readings and potential risk of damage to fistula) and entered into the electronic patient database (proton). For comparative purposes results were contrasted with the published UK targets for blood pressure in HD patients (Mactier 2007).

2.6.7 Medications

Due to the nature of the disease, polypharmacy in HD patients is common place. However the study only examined changes in medications considered to have a direct relevance to the intervention, eg could affect or influence outcomes or in turn be affected by exercise. The unit's electronic patient records system (proton) updated by the unit Pharmacist on a monthly basis was used to obtain this information.

The number, dose and type of antihypertensives and phosphate binders were recorded at each time point. Administration of IV Iron and corticosteroids were also considered. In addition the weekly prescribed dose of erthyropoiesis stimulating agent (ESA) darbepoetin alfa was recorded. This was also used to calculate a dose-response relationship between ESA and haematocrit (ESA/Hct) as an index of responsiveness to ESA (Gunnell et al 1999, Kalantar-Zadeh et al 2003b).

2.7 EXERCISE INTERVENTION

The exercise intervention was designed to minimise any barriers considered likely to adversely affect participation and adherence to the exercise programme. Exercise took place during dialysis, allowing patients the opportunity to exercise three times a week. Exercise was undertaken in the first two hours of the dialysis session to avoid cardiovascular decompensation that may preclude exercise (Moore et al 1998, Kouidi 2002, Koufaki et al 2002, Daul et al 2004).

Prior to the commencement of the study a series of educational and orientation sessions were run for dialysis staff. The sessions focused on explaining the rationale of the study, the exercise programme, precautions and contraindications for exercise (Table 2.3), possible changes that may occur (weight, blood pressure), how to use and move the equipment, their expected role and responsibilities within the study. Their expected role and responsibilities were positioning the cycle in front of patients, assisting in setting the clock if necessary, completing the exercise log, taking and sending the additional blood sample (leptin) to the laboratory.

The first exercise session for each patient was individually supervised by the Investigator. There after one weekly exercise session (Wednesday or Thursday) was individually supervised by the Investigator to allow a review of and to encourage progression. The other two sessions were conducted under general supervision of the dialysis staff. Patients were encouraged to follow the protocol and maintain the correct level of intensity during the other two sessions.

Table 2.3: Precautions and contraindications for exercise

Reasons to discontinue exercise and re-evaluate medical status/exercise programme	When too tired to keep up the effort level, If there is unusual shortness of breath, If there are chest pains, if there is nausea, If the individual experiences irregular or rapid heart beats, if the individual experiences leg cramps or complains of being dizzy/light headed during exercise or if experience muscle/joint pain
Reasons not to commence exercise and to request review of medical status	Temperature > 38^{o}C If a dialysis session has been missed If medically unstable-chest pain, dyspnoea, difficulties with vascular access Symptomatic low blood pressure
Reasons to slow down	When the effort feels very hard or very, very hard When breathing is too hard to talk When muscles are sore the next day Not fully recovered one hour after exercise

(Adapted from '*A guide for the people on dialysis'* by the Life Options Rehabilitation Advisory Council and Miller et al 2002).

The first exercise session with each patient included induction and orientation of the cycle; how to use the monitor and how to adjust the resistance on the pedals to increase intensity. They were also provided with an explanation of the levels of the exercise programme and the Borg RPE scale. Patients were advised to wear loose fitting, light indoor clothing and comfortable shoes for subsequent sessions.

An exercise log was produced and incorporated into each patient's individual dialysis record. For each exercise session dialysis staff were expected to record the duration, distance cycled, level of resistance, pre/post exercise heart rate, blood pressure and any comments or problems. For easy reference the exercise protocol, precautions for exercise and ratings of perceived exercise (RPE) were posted on the dialysis unit notice board.

To provide ongoing motivation and interest for patients, laminated copies of cycle routes in Fife were produced which patients could select and plot the distance they 'travelled'. The dialysis unit notice board was also used to display a map of Europe. Fife was marked as the starting point on the map and the combined distances travelled by patients were plotted on a monthly basis.

The appointment of an exercise ('Champion') liaison Nurse was possible as a consequence of funding from the British Renal Society (equivalent of 0.2 WTE for 1 year). This individual was the first contact in the absence of the Investigator for queries from dialysis staff and patients; they assisted in altering transport arrangements and contributed to the general day to day supervision of programme.

2.7.1 Cycle ergometer

The availability of specific cycle ergometers for use within the dialysis unit is limited. In order for the study aims to be achieved, the ergometer had to be easy to use, be practical in design and to be of a size that could easily be moved around the unit between patients and be stored within the confines of the unit. The dialysis staff had indicated a preference for an ergometer that secured to the floor rather than the chair should access to patients in an emergency be required. It was also felt that an ergometer which was compatible with the unit's existing type of dialysis chair would assist in integrating exercise into the unit.

The most commonly used cycle ergometer in exercise studies to date has been the Monarch Rehab Trainer 881E. However, this bike was not directly compatible with the units existing dialysis chairs. This latter aspect would require additional adaptations to be made which in turn would potentially require the bike to be

secured to the chair when in use. Therefore, this made the cycle less practical to use and more difficult to both move between patients and to store between sessions. The Monarch was, therefore, ruled out as it was not considered a feasible, realistic and practical option for what would be a largely unsupervised exercise programme with responsibility on the dialysis staff and one which was aiming to be incorporated into routine care.

The chosen cycle ergometer was the Champ-cycle (Champion Manufacturing, Elkhart, IN) which was directly compatible with the existing dialysis chairs, negating the need for any adaptations (Figure 2.1). The cycle ergometer could also be secured to the floor and was described as being light and compact in size (maximum floor space required is 40'' x 20'', weight 55lbs). The control panel (clock) and resistance control device were easily accessible by the patient (within arms reach), which promoted a degree of self care and reduced the involvement of dialysis staff. Booster cushions were available for those patients who required them. Booster cushions were used to ensure maintenance of postural control during exercise. A total of five ergometers were purchased for use within the study.

It should however be highlighted that the work load of the chosen ergometer cannot be calibrated. Therefore a potential for variations in exercise intensity at a given resistance level between the five ergometers existed. This issue was addressed by numbering each ergometer and assigning a particular ergometer to an individual patient for the duration of the study.

Figure 2.1: Champ cycle ergometer in situ

(Source: Champion Manufacturing, Elkhart, IN)

2.7.2 Exercise protocol.

The principles of any systematic exercise programme should address the appropriate mode, duration, intensity, frequency and progression with the view that the interaction of these variables, results in a cumulative overload to which tissues must adapt. These principles are considered to apply for persons of all ages and fitness levels, regardless of the presence or absence of risk factors and disease (ACSM 2000).

The exercise protocol used in this study was adapted from the 'Easy Bike Program (Karmiel 1995, Karmiel 1996)'. This programme was developed for HD patients by an American College of Sports Medicine health and fitness instructor and included consideration of mode, duration, intensity, frequency and progression.

The exercise protocol aimed to encourage participation of low functioning patients and/or those with significant comorbidities (including cardiovascular). The starting level was considered to be appropriate for the majority of patients and confer minimal risk to the majority of the dialysis population. Progression was broadly applicable, easy to understand and realistic. This was considered important in view of the reduced level of supervision (Table 2.3).

The programme (level 1) began at a very low intensity, defined as < 35% HR_{max} (RPE <10) and gradually increased to a moderate intensity (level 3) defined as 55-69% HR_{max} (RPE 12-13), the level at which it is considered that cardiorespiratory benefits are obtained. The aim of level 1 was to encourage participation, build confidence and avoid cardiovascular side effects or orthopaedic injury that can occur with higher intensity programmes (ACSM 2000). Completion of level 1 was expected to take 2 months. Level 2 continued to extend the time to the desired final goal of 30 minutes per session with an expectation that it would take 5 weeks to complete this level. Level 3 conformed to the components of an exercise programme as described by ACSM, with a warm up period (5-10 minutes), an endurance phase/stimulus (20-30 minutes) and a cool down period (5-10 minutes). It was expected that patients would reach this level after 12 weeks. The purpose of the warm up was to reduce the susceptibility to musculoskeletal injury. The purpose of the cool down was to provide a gradual recovery from the endurance/stimulus phase; permitting appropriate circulatory adjustments, a return of blood pressure and heart rate to pre-exercise values, enhanced venous return and reduced the potential for post exercise hypotension or dizziness (ACSM 2000).

Patients who missed up to 6 (2 weeks) consecutive exercise sessions due to medical reasons or personal, recommenced at the same level and any patient who

missed up to 12 (1 month) consecutive sessions restarted the programme. This approach was based on (but modified to be more conservative), the premise that in healthy individuals during periods of inactivity, initial improvements in cardiorespiratory fitness decrease by 50% after 4-12 weeks of detraining (ACSM 2000).

Table 2.3: Exercise protocol

Level 1 (Low intensity)	First session: 3 minutes of easy cycling (RPE 7-9) with no resistance. Subsequent sessions; add 1 minute as able and continue at easy cycling pace (RPE 7-9), increase resistance if required to achieve RPE 7-9 each session. Progress to 20 minutes and maintain for 2 weeks (6 sessions) then progress to Level 2.
Level 2 (Low intensity)	Progress from 20 minutes by adding 1 minute per session, easy cycling pace (RPE 7-9). If required increase the resistance on bike pedals to achieve and maintain RPE of 7-9. Progress to 30 minutes and maintain for 2 weeks (6 sessions) and then progress to Level 3.
Level 3 (Moderate Intensity)	Maintain 30 minutes of cycling Warm up for first 5 minutes –easy cycling pace as above (RPE 7-9) Middle 20 minutes –Each session aim for somewhat hard cycling pace (RPE 12-13) by increasing resistance on bike pedals as required. Cool down for 5 minutes- easy cycling pace as above (RPE 7-9)

2.7.2.1 Ratings of perceived exertion for prescribing & monitoring exercise

There is some concern that non-supervised exercise may jeopardise the safety of a patient due to potentially uncontrolled exercise intensities (Birk & Birk 1987) or that patients will fail to exercise at an effective level of intensity to elicit and sustain

benefits. However there are several widely used and well established benchmarks of exercise intensity that can be used to avoid this. The most commonly used are percentages of VO_2max, percentages of maximal heart rate or ratings of perceived exertion (RPE).

Due to the study aims and design, the use of VO_2 max was not an option. In addition the use of target heart rates in dialysis patients is unreliable as they have abnormal exercise heart rate responses, are frequently prescribed medications that affect their heart rate response (eg β-Blockers). Furthermore an individual's heart rate response may be influenced by fluid status (Eston & Connolly 1996). Therefore, in what would be an exercise intervention that was primarily delivered with only general supervision, ratings of perceived exertion (RPE) (Borg 1998) were used to regulate and progress individual levels of intensity, with a view to facilitating the beneficial conditioning effects of exercise and avoiding complications (Foster et al 2001, Dual et al 2004).

RPE, also known as the work effort scale, is an accepted and well documented proxy measure of physiological strain used to ensure the appropriateness of levels of exercise stress in the conditioning of individuals. It is also a method that has been shown to correlate with various physiological measures such as heart rate and blood lactate concentrations (Borg 1998). Furthermore it is considered to be a practical and easily understood concept in individuals of all fitness levels (Borg 1998, ACSM 2000). The scale ranges from 6 to 20 with effort descriptions at each level (6 is rest) (Figure 2.3).

The RPE was evaluated on a weekly basis as part of the individually supervised exercise session. Verbal instructions as per Borg (1998) were used on each

occasion. The RPE was evaluated at 3 minutes into the exercise session at level 1 and 2. At level 3 the RPE was evaluated 3 minutes into the warm up period, 3 minutes into the 20 minute endurance/stimulus period and then 3 minutes into the cool down period. This approach was used to ensure that a 'steady state' with respect to oxygen delivery/utilisation had been achieved by the cardiopulmonary system, as there is some suggestion that at approximately 3 minutes central and peripheral cues are integrated into a more accurate and undifferentiated RPE (Birk & Birk 1987). At level 3 if patients reported an RPE <12 in the endurance/stimulus period they were instructed to increase the level of resistance on the cycle pedals until they reported an RPE of 12-13 on the Borg 6-20 scale (Borg 1998). They were then asked to maintain this level of resistance for the next two exercise sessions.

6	No exertion at all
7	
	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 2.3: The Borg RPE Scale (Borg 1998)

2.8 STATISTICAL ANALYSIS

Whilst ideally a power analysis should be prospectively performed in order to decrease the rate of both type I and type II errors, this was not possible. There were no previous intradialytic HD exercises studies utilising the selected functional outcome measures (which were considered to be the primary outcomes). In addition, the proposed low to moderate intensity exercise intervention had not been previously used in an older HD population with an anticipated higher level of co morbidity. These factors therefore prevented estimations of effect size.

Independent samples t-tests were used to examine differences between the intervention and control group at recruitment. One sample t-tests were used to examine differences between normative data and the recruited population when the distribution of the normative data was unknown.

A one way repeated measures analysis of variance (RM ANOVA) was performed to examine within group changes over time. The sphericity of the data was tested using Mauchly's test. Where variation in the data was not consistent as indicated by the Mauchly's test, the Greenhouse-Geisser adjustment was used to reduce the likelihood of type II errors.

Where RM ANOVA reached significance, post hoc tukey tests were used to identify significant differences between time points. The use of a post hoc Tukey test corrects for the increased probability of making a type I error which would ordinarily occur if multiple t-tests were used.

Pearson's two tailed correlation was used to examine associations between significant changes in function, quality of life, nutritional status and clinical status. Prior to performing Pearson's correlations, normal distribution of the data was confirmed using the Shapiro-Wilk test.

Statistical analysis was performed using the statistical package for social sciences (SPSS versions 16.0 and 17.0). Results with p values of <0.05 were considered significant.

CHAPTER 3: VALIDATION OF BIOELECTRICAL IMPEDANCE ANALYSIS & ANTHROPOMETRY

3.1 INTRODUCTION

Upper limb anthropometric measurements of single sites such as mid arm circumference (MAC), tricep skinfold thickness (TSF) and mid arm muscle circumference (MAMC), have provided the cornerstone of body composition assessment for many years in the HD population. However, little work has been done to examine the agreement of these single site measurements with an accepted reference method such as dual energy x-ray absorptiometry (DXA). In addition, much of the work that has been done, has focused on the prediction of FM derived from skinfold measurements at multiple sites (Kamimura et al 2003a Kamimura et al 2003b) rather than the prediction of FM derived single sites.

Furthermore, it would appear that the anthropometric prediction of FFM and agreement with an accepted reference method has largely been neglected with the exception of one study by Cooper et al (2000). However, this study included HD, PD and transplant patients and the prediction of total FFM was calculated from body weight and percentage body fat results initially derived from multiple skinfold thickness measurements.

Moreover, there is a distinct absence of work in the HD population examining the agreement of lower limb anthropometric measurements such as calf circumference (CC), calf skinfold (CSF), calf muscle circumference (CMC), which may provide better predictors of total FM and FFM along with a concomitant indicator of

functional status (Stewart, Stewart & Reid 2002, Newman et al 2003, Rolland et al 2003).

As highlighted in chapter 1 (Section 2.5.4), there is a growing interest in the use of bio-electrical impedance analysis (BIA) for the prediction of total body composition in the HD population. This is because BIA is considered to be a simple, practical and time efficient method which can potentially provide information on body water, fat, fat free mass and body cell mass (Ho et al 1994, Jaegar & Mehta 1999, Chamney et al 2002, van de Kerkhof et al 2004, Barbosa-Silva 2008). To date, much of the interest has been in the estimation of total body water (TBW) or extracellular water (Ho et al 1994, Chertow et al 1995, Woodrow et al 1996, Chamney et al 2002, Yu et al 2006) and the timing of measurements (Donadio et al 2005) with less work focusing on the prediction of total FM (Kamimura et al 2003a, Kamimura et al 2003b) or total FFM (Donadio et al 2008).

There are different types of bioelectrical impedance monitors available measuring at different frequencies. Two of the above studies used mono (single) frequency BIA at a fixed frequency of 50 KHz (Kamimura et al 2003a, Kamimura et al 2003b), and one study compared multifrequency bioelectrical impedance with mono (single) frequency methods (Donadio et al 2008). The use of mono (single) frequency BIA in HD patients has been criticised, because mono (single) frequency BIA is considered to be unreliable in quantifying extracellular water (ECW) and thus TBW (Woodrow et al 1996, Chumlea 2004). It also cannot distinguish between ECW and intracellular water (ICW) and is therefore unable to provide reliable estimates of FFM and body cell mass (BCM) (Earthman et al 2007). These criticisms, therefore, led to the recommendation for the use of more expensive and complex types of bioelectrical impedance monitors (Cha et al 1995, Chumlea 2004). This is because these

monitors are considered more reliable in quantifying BCM as they operate at multiple frequencies and can therefore differentiate between the proportions of intra and extracellular water (Cha et al 1995, Chumlea 2004). However, it has been suggested by some authors that the results with multiple frequency bioelectrical impedance are mixed and that further validation, particularly in altered hydration states such as CKD is required (Kyle et al 2004, Earthman et al 2007). Added to this, previous work in surgical patients (Hannan et al 1995) has questioned the value of monitors operating at multiple frequencies versus those operating at fixed dual frequencies. The study by Hannan et al (1995) found that in comparison to dual frequency BIA operating at two fixed frequencies of 5 & 200 KHz only, BIA operating at multiple frequencies provided no further accuracy in the assessment of ECW and TBW. There are also distinct practical advantages of a dual frequency BIA analyser over those operating at multiple frequencies in terms of reduced costs and reduced time to acquire and calculate results (Hannan et al 1995). Dual frequency BIA operating at these fixed frequencies has not, however, been used in a HD population, therefore requires to be validated against an accepted reference method such as DXA.

DXA has increasingly become an accepted and commonly used reference method for validation studies; despite the view by some that DXA as a reference method is not entirely valid (Jebb et al 1995, Pietrobelli et al 1998). This is because one of the known limitations of DXA is the accuracy of DXA measurements and in particular those of FFM being affected by variations in TBW (Formica et al 1993, Georgiou et al 1997, Pietrobelli et al 1998) and that in the HD population due care and attention to the timing of DXA measurements is therefore required (Stenver et al 1995, Abrahamsen et al 1996, DeVita 1999, Pupim and Ikilzer 2004). However, despite this it is considered for HD populations and others to be more time efficient,

practical, less onerous, invasive and costly method in comparison to other 'gold standard' methods such as densitometry or IVNA (Van der Ploeg et al 2003, Chumlea 2004, Rigalleau et al 2004, Fouque et al 2007).

The aims of the study were:

1. To investigate the agreement of upper and lower limb anthropometric measurements with DXA.

2. To investigate the agreement of total FFM and FM estimated by dual frequency BIA (DFBIA) with DXA.

3.2 SUBJECTS AND ETHICAL APPROVAL

Ethical approval was obtained from QMU ethics committee and Fife NHS ethics committee to recruit a subgroup of patients who had been recruited to the exercise study, but who had not yet commenced the study.

Inclusion criteria for this aspect were similar to that of the main study and were as follows: On maintenance dialysis for at least 6 months and younger than 80 years of age.

Exclusion criteria for this aspect of the study were as follows: Clinically significant signs of oedema or ascites or limb amputations, as these conditions were likely to affect the accuracy of the measurements being taken.

3.3 METHODS

It is common practice that the timing of measurements of body composition in the HD population are standardised to when a patient is as close to their 'dry' weight, which is defined as the lowest weight at the end of dialysis that patients can tolerate without symptoms such as cramps and hypotension (Guida et al 2004). Measurements taken at this time are considered to minimise any potential errors associated with changes in TBW (Di Iorio et al 2004, Pupim and Ikilzer 2004) and therefore provide a more accurate assessment of body composition. However, whilst it was possible to undertake the anthropometric and the DFBIA measurements immediately post dialysis, it was not possible to undertake the DXA scans at this time. This was due to either late dialysis appointments or the duration of the patient's dialysis session precluding the ability to perform the DXA scans after dialysis. It was also due to the location of the DXA scanner on another hospital site requiring additional transportation arrangements. As a consequence, the DXA scans had to be scheduled for the following non dialysis (interdialytic) day. Therefore, another set of DFBIA and anthropometric measurements were taken immediately after the DXA scan with a view that any potential increases in TBW could be identified and the impact explored.

All anthropometric measurements were taken by the author, a trained level 3 ISAK (Instructor) anthropometrist. The authors' known technical error of measurement was derived prior to the commencement of the study from repeated measures on 20 subjects were as follows: Mid arm circumference =0.05cm (0.2%), tricep skinfold =0.1mm (0.74%), calf circumference =0.07cm (0.19%) and calf skinfold =0.11mm (0.93%). The intraclass correlation coefficient for these measurements was 1.0. ISAK methodologies were followed where relevant (Chapter 2, section 2.5.3).

The measurements were as follows: Height (Ht) in metres, weight (Wt) in kilograms, mid arm circumference (MAC) (cm), tricep Skinfold (TSF) (mm), mid calf circumference (CC) (cm), mid calf skinfold (CSF) (mm). Mid arm muscle circumference (MAMC) (cm) and calf muscle circumference (CMC) (cm) were then derived from the following equation (Martin et al 1990):

$$\text{MAMC/CMC (cm)} = \text{MAC/CC (cm)} - (3.14 \times \text{TSF/CSF (cm)})$$

Height was measured using a portable wall stadiometer (range 60-220cm) measuring to 0.1cm, weight was measured to the nearest 0.1Kg using portable secca scales, circumferences were measured using a flexible steel tape measure (Lufkin W606PM) and skinfold thicknesses were measured to 0.2mm using Harpenden skinfold calipers (Harpenden). Calibration of the relevant equipment occurred prior to the commencement of this validation study and the same equipment was used for both sets of measurements.

BIA measurements were taken by the author on both occasions, using a dual frequency BIA monitor (DualScan 2005-Bodystat UK) operating at the previously defined optimal frequencies of 5 kHz and 200 kHz (Hannan et al 1995). The BIA measurements were taken 15 minutes post dialysis (Dumler & Kilates 2000, Di Iorio et al 2004, Jankowska, Debska-Slizien & Rutkowski 2006) and then repeated on the following interdialytic (non-dialysis day) immediately after patients had attended for the DXA scan. Both sets of BIA measurements were conducted in what was considered an ambient environment of 22^{o}C (Kyle et al 2004), with patients in the supine position, arms and legs apart. Two electrodes (>4cm^{2}) were placed on both the right hand and foot or on the side contralateral to the arteriovenous fistula (Woodrow et al 1997, Dumler & Kilates 2000).

Regression equations developed by Hannan et al (1995) at the fixed frequencies of 5 kHz and 200 kHz were used to estimate ECW and TBW respectively (Chapter 2 section 2.5.4). Although it is recognised that these regression equations were not developed in a dialysis population, in the absence of other validated regression equations at the fixed frequencies of 5 kHz & 200 kHz, these equations were deemed to be appropriate. This was because it was postulated that the pattern of changes in TBW in the original study group would be similar to those seen in a HD population. In the absence of any other known equations, total FFM, FM were derived as follows:

FFM (kg) = TBW (L)/0.732

FM = Body weight (kg) - FFM (Kg);

ICW (L) = TBW (L)-ECW (L)

Whole body DXA scans were conducted on the morning of the patients interdialytic (non-dialysis day) using a GE Lunar Prodigy Scanner (scan time 5 minutes, radiation dose: 0.04mRem, precision <1% for total tissue) (GE Medical Systems). The manufacturers computer software was used to quantify FFM (lean soft tissue mass + bone mineral content) (Kg) and FM (Kg). Patients were asked to wear similar light indoor clothing as worn to their HD sessions, but with any materials that could attenuate the x-ray beam removed eg jewellery, watches and belts.

Data was analysed using SPSS version 16.0 and statistical tests were performed on the data as follows: paired t-tests to examine any differences in the measurements between the two days; Pearson's correlations to examine associations between BIA, anthropometric measurements and DXA with normal distribution of the data having been confirmed using the Shapiro-Wilk test. Results with p values <0.05 were

considered significant. In addition Bland Altman analysis was used to examine limits of agreement between estimates of total FM and FFM derived from BIA and DXA.

3.4 RESULTS

A total of 19 HD patients (9 male, 10 female) volunteered to take part. The characteristics of this study population are provided in Table 3.1. Notably based on the mean BMI; the group would be perceived to be a normally-well nourished group (20-25Kg/m^2) (WHO 1995). There was also a small but statistically significant difference ($p<0.01$) observed between the immediate post dialysis weight and the interdialytic weight.

Table 3.1: Characteristics of the study population

	Mean ± SD
Age (years)	54.06 ± 11.06
Post dialysis weight (Kg)	69.76 ± 15.62
Interdialytic weight (Kg)	70.10 ± 15.59*
Height (m)	1.66 ± 0.16
BMI (Kg/m^2)	25.12 ± 4.89

*significantly different from post dialysis weight ($p < 0.01$)

Table 3.2 summarises the results for the anthropometric measurements. There were no significant differences in the upper limb anthropometric measurements taken immediately post dialysis and on the next (interdialytic) day. There was a small, but statistically significant difference in the lower limb measurements of CC and CSF between days. The DFBIA results demonstrated small, but significant differences between days for FFM, TBW and ECW.

Table 3.2: Summary of anthropometric, DFBIA and DXA measurements

	Post Dialysis	Interdialytic
MAC (cm)	29.7 ± 4.6	29.8 ± 4.7
TSF (mm)	16.5 ± 4.7	16.3 ± 4.5
MAMC (cm)	24.6 ± 3.7	24.7 ± 3.7
CC (cm)	35.0 ± 3.9	35.4 ± 3.9*
CSF (mm)	12.7 ± 6.11	13.4 ± 6.2 *
CMC (cm)	31.0 ± 3.9	31.2 ± 4.0
DFBIA -FFM (Kg)	46.2 ± 9.55	47.4 ± 9.78 *
DFBIA-FM (Kg)	23.5 ± 8.89	22.7 ± 8.6
DFBIA-TBW (L)	33.8 ± 7.0	34.6 ± 7.1 *
DFBIA-ECW (L)	16.5 ± 2.7	17.2 ± 2.8 *
DFBIA-ICW (L)	17.3 ± 4.4	17.4 ± 4.4
DXA-FM (Kg)	-	21.9 ± 10.1
DXA-FFM (Kg)	-	48.8 ± 9.6

(Values are presented as mean ± SD, * $p < 0.05$ paired t-test)

Table 3.3 provides a summary of the correlations between the anthropometric, DFBIA measurements and DXA for the measurements taken immediately post dialysis and on the interdialytic day. There were significant and consistent levels of agreement for all of the anthropometric and DFBIA measurements between days.

Table 3.3: Summary of associations between anthropometric measurements and DFBIA versus DXA- FM (DFM) or DXA-FFM (DFFM)

	Post dialysis	Interdialytic
	r	*r*
DFM: MAC	0.920**	0.914**
DFM: TSF	0.700**	0.773**
DFM: CSF	0.550*	0.482*
DFM: DFBIA-FM	0.972**	0.980**
DFFM: CC	0.698**	0.698**
DFFM: MAMC	0.545*	0.538*
DFFM: CMC	0.839**	0.833**
DFFM: DFBIA-FFM	0.969**	0.972**

** $p < 0.01$, * $p < 0.05$

CMC and CC demonstrated a stronger association with DXA-FFM than MAMC (Figures 3.1, 3.2, 3.3). MAC and TSF demonstrated a stronger association with DXA-FM than CSF (Figures 3.4, 3.5, 3.6). There were also significant consistent associations between DFBIA-FFM, FM measurements and DXA-FFM, FM measurements (Figures 3.7 & 3.8).

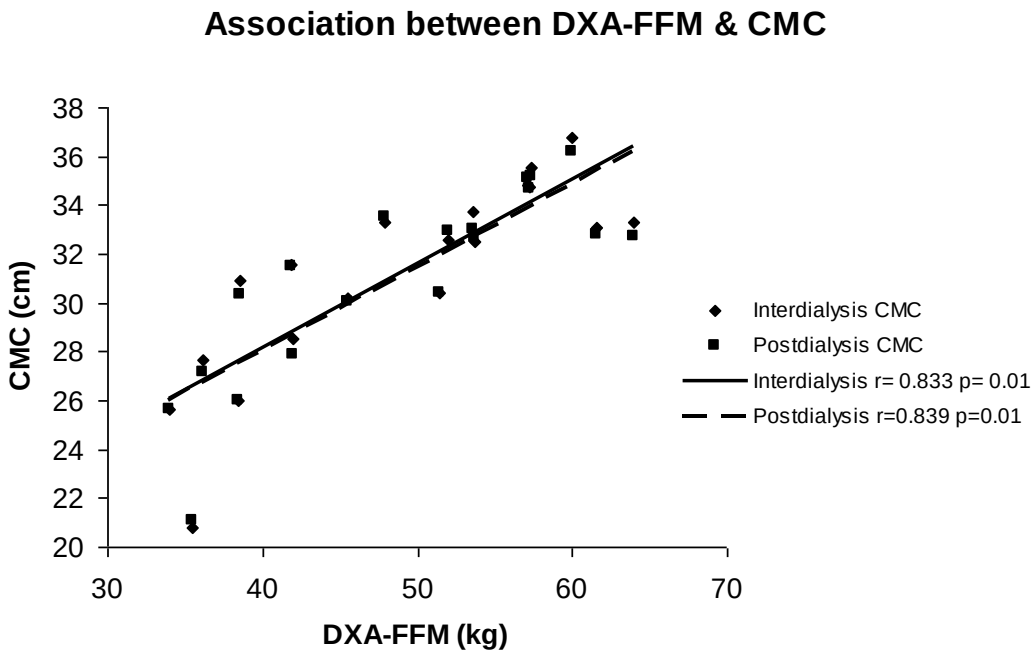


Figure 3.1 Association between calf muscle circumference (CMC) and DXA-FFM

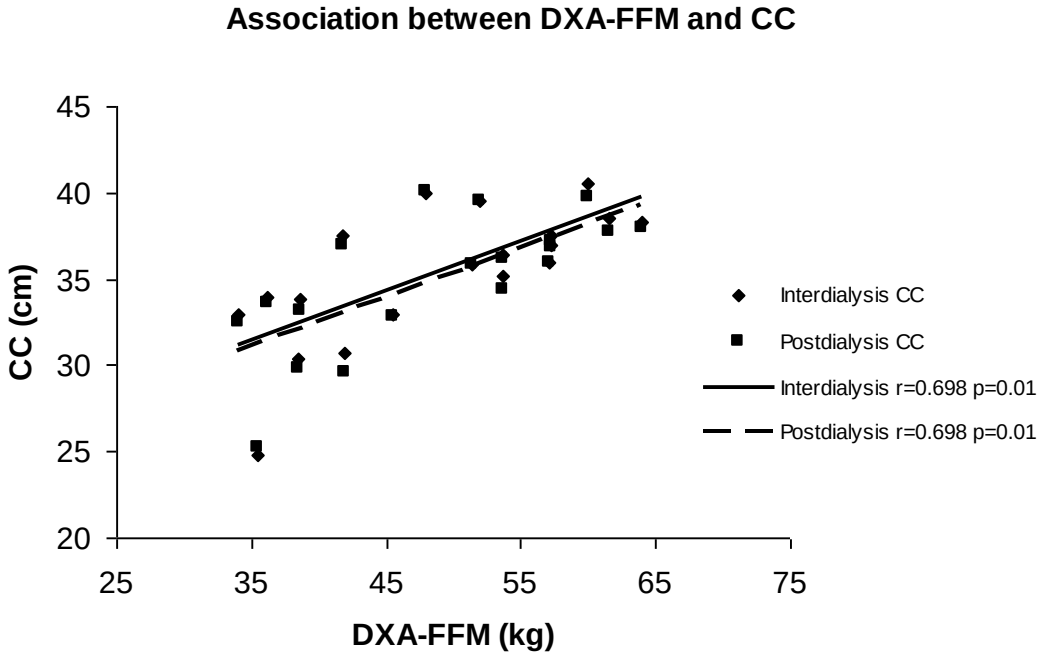


Figure 3.2 Association between calf circumference (CC) and DXA-FFM

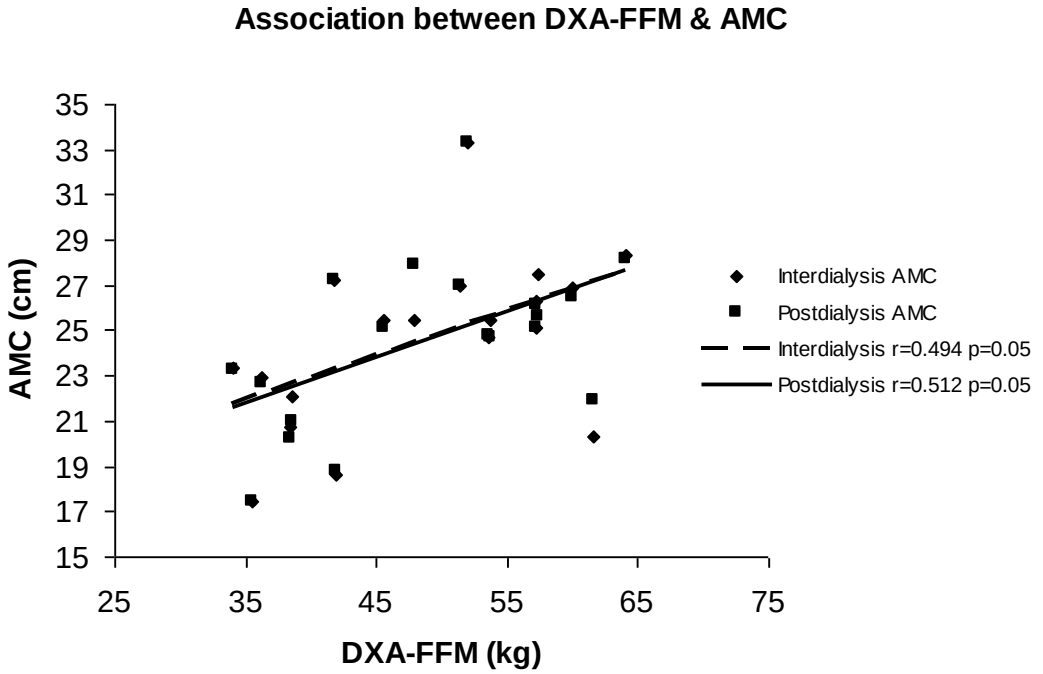


Figure 3.3 Association between mid arm muscle circumference (MAMC) and DXA-FFM

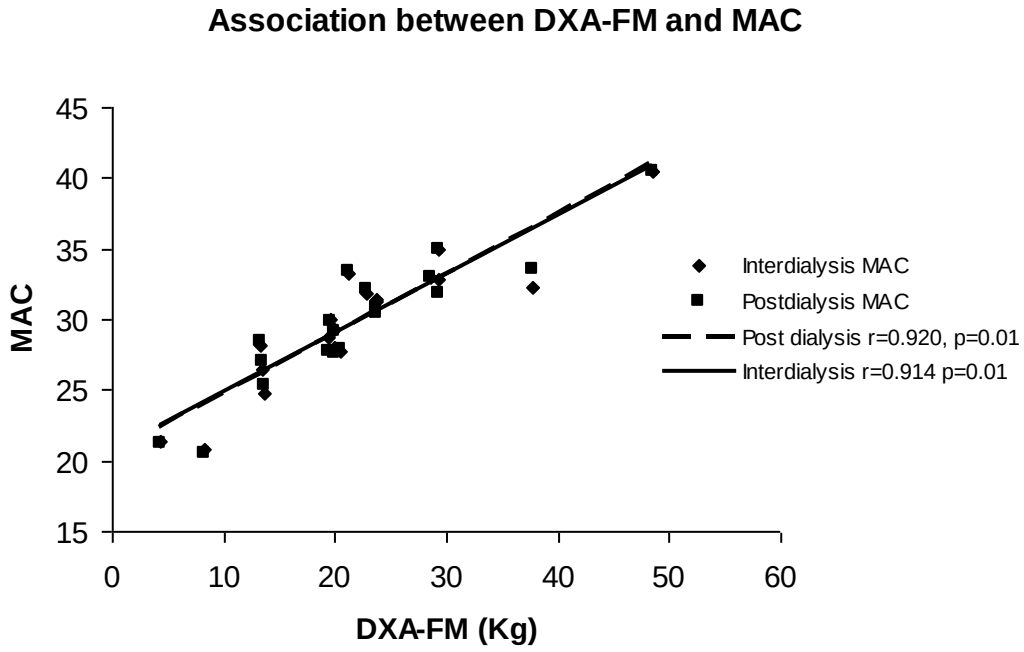


Figure 3.4 Association between mid arm circumference (MAC) and DXA-FM

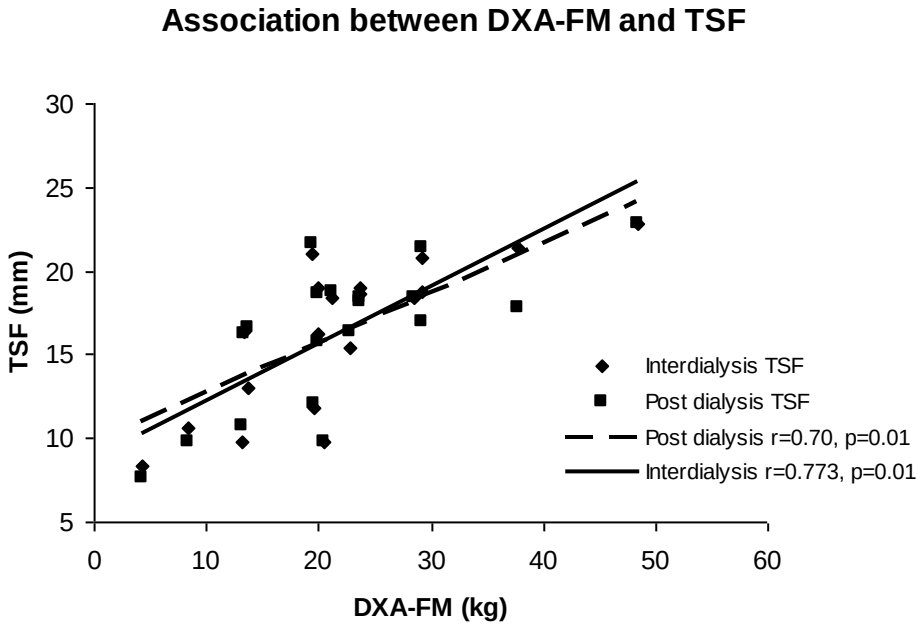


Figure 3.5 Association between tricep skinfold thickness (TSF) and DXA-FM

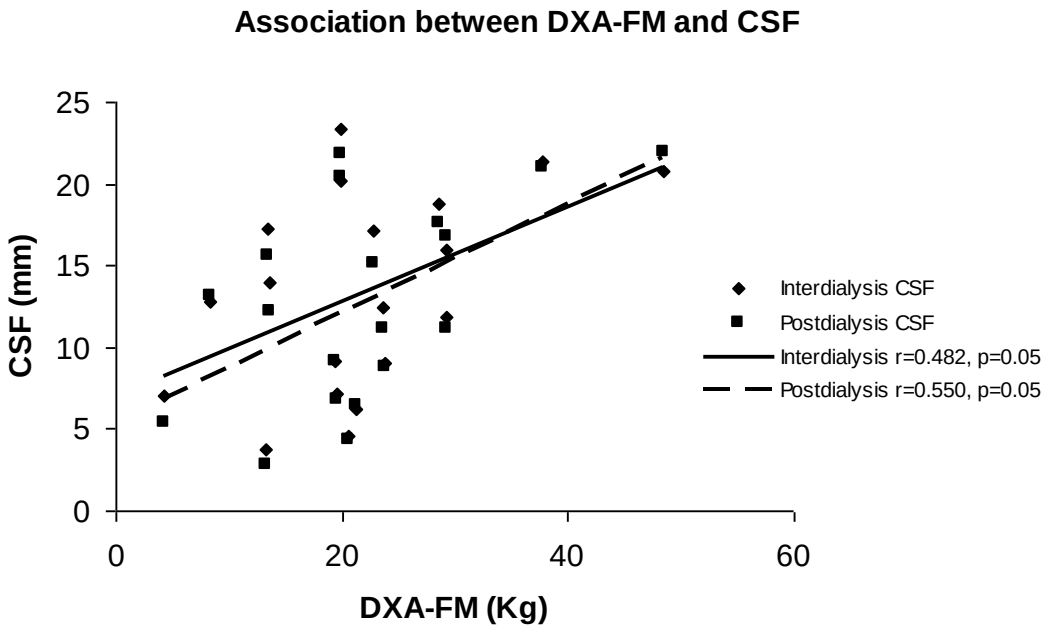


Figure 3.6 Association between calf skinfold thickness (CSF) and DXA-FM

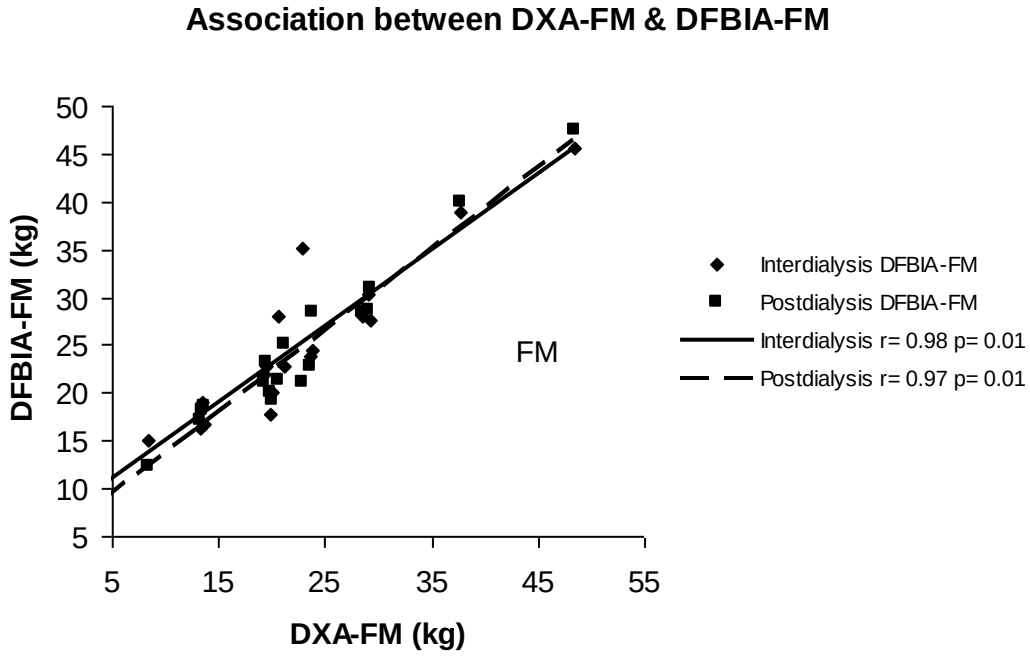


Figure 3.7 Association between DFBIA-FM and DXA-FM

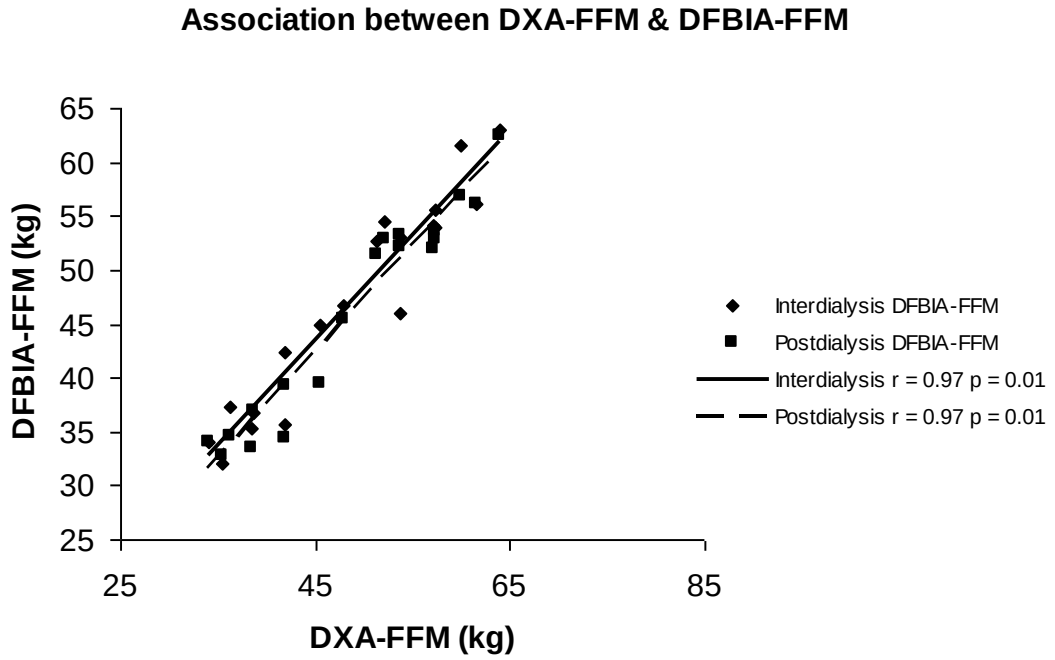


Figure 3.8 Association between DFBIA-FFM and DXA-FFM

As DFBIA provided comparative total FFM and FM data, further analysis of this data was undertaken to examine the limits of agreement between DFBIA and DXA (Figures 3.9, 3.10, 3.11 & 3.12). The results for DFBIA-FFM measured on either the interdialytic day or post dialysis show that 95% of the values fall within the upper and lower limits of agreement. The results for DFBIA-FM show that 100% of the values fall within the upper and lower limits of agreement. The DFBIA-FM results also demonstrate that on either day there is evidence of a proportional error.

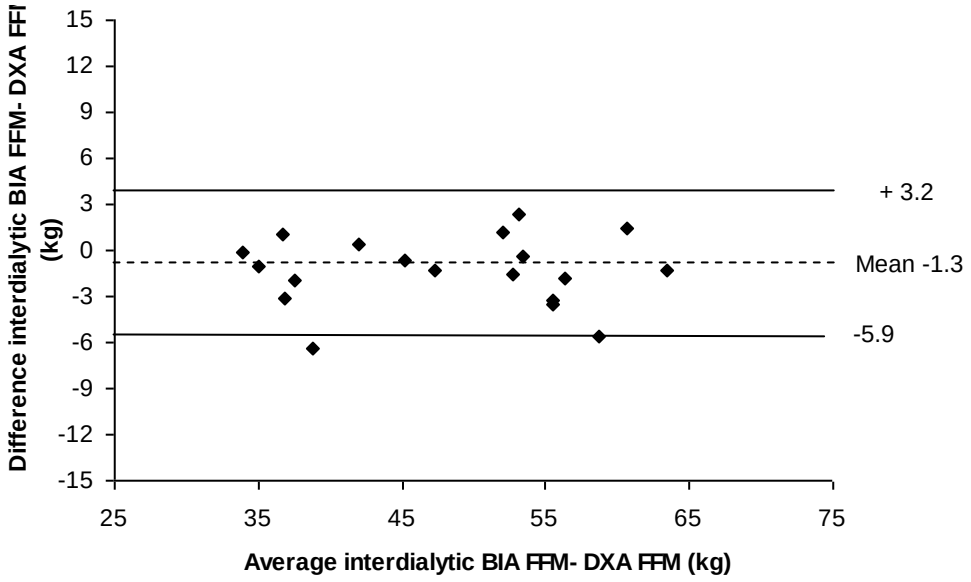


Figure 3.9: Limits of agreement for interdialytic FFM measured using DFBIA with FFM measured by DXA. Mean = -1.30kg, upper limit=3.2kg, lower limit= -5.9kg

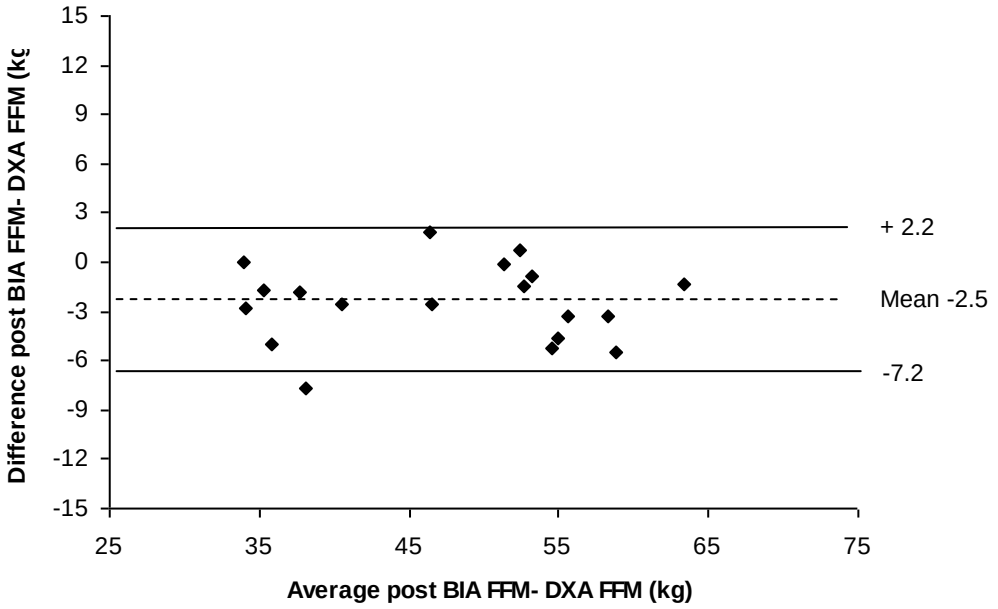


Figure 3.10: Limits of agreement for post dialysis FFM measured using DFBIA with FFM measured by DXA. Mean =-2.5kg, upper limit =2.2kg, lower limit =-7.2kg

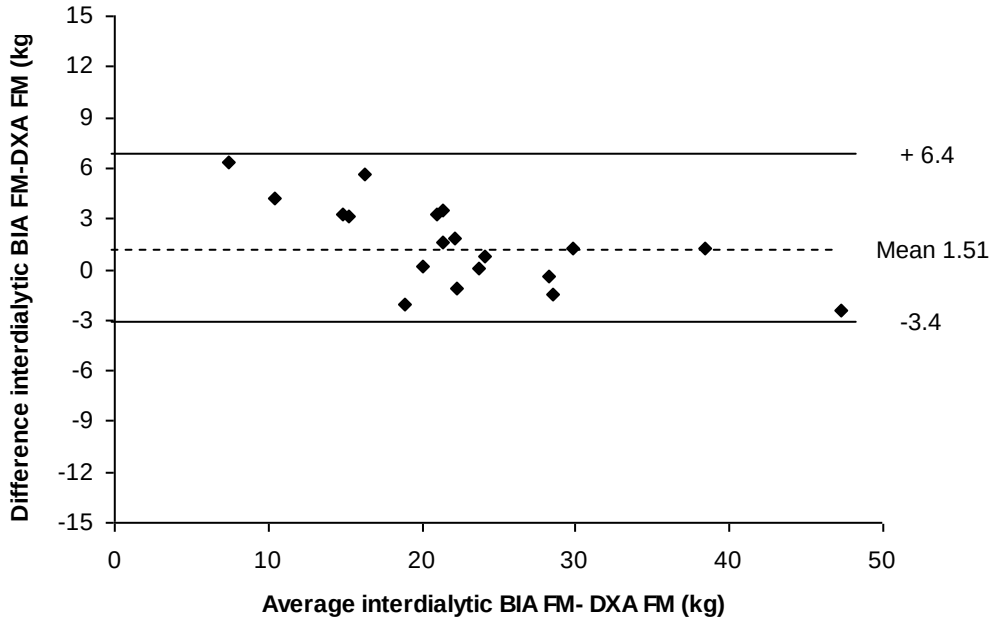


Figure 3.11: Limits of agreement for interdialytic FM measured using DFBIA with FM measured by DXA. Mean =1.51kg, upper limit = 6.4kg, lower limit=-3.4kg

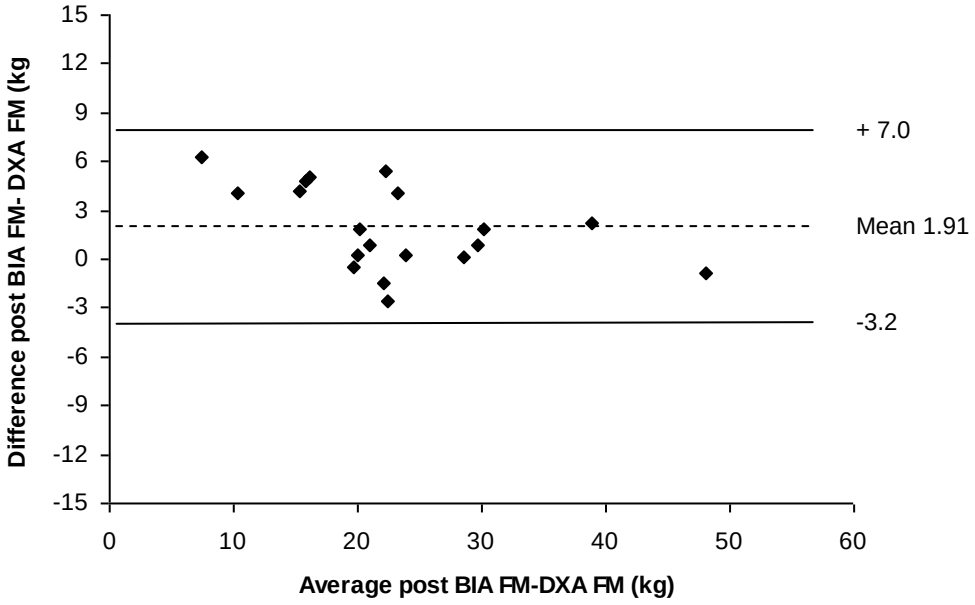


Figure 3.12: Limits of agreement for post dialysis FM measured using DFBIA with FM measured by DXA. Mean = 1.91kg, upper limit = 7.0kg, lower limit =-3.2kg

3.5 DISCUSSION

The results demonstrate that on either day the commonly used anthropometric measurements of single sites (MAC, TSF) show a strong correlation with total body FM derived from DXA analysis. The results also demonstrate that the commonly used measurement to predict total FFM (MAMC) demonstrates a poorer level of correlation with FFM derived from DXA in comparison to the lower limb measurements of CC and CMC. This latter stronger correlation appears to have only been previously observed in a study of male cadavers (Martin et al 1990) and may be as a result of calf FFM proportionally making a greater contribution to total FFM than upper arm FFM (7.5% versus 2.8% in the present study). It is, therefore, considered that these findings further promote the use of lower limb anthropometry to reflect and monitor changes in FFM.

There was a small, but statistically significant difference in results between days for the CSF and CC measurements, the latter which was also outwith the author's technical error of measurement. This could be explained by an increase in TBW (ECW) which is confirmed by both the increase in body weight and by the DFBIA measurements between days. Previous studies have shown that the pattern of change in TBW (ECW) has a greater effect on lower limbs than upper limbs (Yu et al 2006, Lee et al 2008). Although the differences between days diid not impact on the results for CMC between days, this suggests that when serial anthropometric measurements of lower limbs are being made, the timing of the measurements must be standardised. However this does not seem to apply to upper limb measurements. From these results the optimal timing would be when patients are as close to their dry weight as possible (ie immediately post dialysis), to minimise the possible affect of changes in TBW (ECW).

In comparison to the anthropometric results, the DFBIA results taken on the interdialytic day versus those taken immediately post dialysis, demonstrate small but statistically significant increases for FFM, TBW and ECW. The only exceptions to this were the FM results. It would seem apparent from the results that DFBIA can detect small differences in TBW and is able to distinguish between changes in ECW and ICW. What is also apparent is that the detected increase in ECW is being interpreted by BIA as an increase in total FFM. This could therefore potentially limit the usefulness of DFBIA in the HD population for tracking changes in body composition, and in particular FFM, overtime. Similar observations have been reported elsewhere (DeVita & Stall 1999) and support the view that BIA measurements must be standardised as per the anthropometric measurements to immediately post dialysis and all other possible methodological steps taken to control for variations in TBW.

Similar to the anthropometric results, the DFBIA FM and FFM results on either day demonstrated a strong and consistent correlation with DXA FM and FFM respectively. The associations found in the present study compare favourably with two other studies in HD patients examining the association of FFM and/or FM derived from BIA with DXA (Kamimura et al 2003a, Donadio et al 2008). The Donadio et al (2008) study, demonstrated correlation coefficients (r) of 0.88 and 0.85 for FM estimated by two types of monofrequency BIA when compared to DXA and a correlation coefficient (r) of 0.75 for FM estimated by multifrequency BIA when compared to DXA. In the same study (Donadio et al 2008), correlation coefficients (r) of 0.92 and 0.91 were observed for the estimation of FFM by two types of monofrequency BIA when compared to DXA and a correlation coefficient (r) of 0.92 for FFM extimated by multifrequency BIA. In the other study (Kamimura et al 2003a) a correlation coefficient (r) of 0.91 was observed for FM estimated by

monofrequency BIA when compared with DXA (FFM was not examined in this study).

In the present study, the levels of agreement for both FM and FFM demonstrate that at a population level the mean differences (± confidence intervals) are better on the interdialytic day (immediately after DXA scan) rather than the post dialysis day. This finding can again be explained by the noted difference in TBW (ECW) between the days and is consistent with other studies (Horber et al 1992, Stenver et al 1995, Pietrobelli et al 1998). Had the DXA scans been performed immediately post dialysis rather than the following interdialytic day it is possible, although not proven, that the post dialysis BIA results would demonstrate similar levels of agreement with DXA.

Despite the above, it appears from the results in the present study that at a population level and at any given time DFBIA will generally underestimate total FFM. This finding is consistent with the study by Donadio et al (2008). In this study monofrequency BIA was found to underestimate total FFM by a mean of 1.65kg and multifrequency BIA was found to underestimate total FFM by a mean of 2.7kg (Donadio et al 2008). The limits of agreement for FFM in the present study also compare favourably with the study by Donadio et al (2008), which were -6.7 to 7.6kg for monofrequency BIA and -10.4 to 9.1kg for multifrequency BIA.

Equally it seems apparent at a population level and at any given time that DFBIA will generally overestimate total FM. This finding is again consistent with the Donadio et al (2008) study, but not the study by Kamimura et al (2003a) study. In the Donadio et al (2008) study monofrequency BIA was found to overestimate total FM by 1.65kg on average and multifrequency BIA was found to overestimate total FM by a mean of 2.8kg. Conversely, in the Kamimura et al (2003a) study monofrequency BIA was

found to underestimate rather than overestimate by an average of 0.39kg. However the limits of agreement for FM which were reported in the Kamimura et al (2003a) study, but not the Donadio et al (2008) study, were similar (-6.1-6.9kg) to the findings in the present study.

Furthermore, the evident proportional error seen in DFBIA-FM results in the present study suggests that DFBIA, at an individual level, is likely to always overestimate, to a greater extent, total FM in those with a lower total body FM and underestimate, to a greater extent, total FM in those with a higher total FM.

3.6 CONCLUSION

From the parameters examined in this study, FM and FFM derived from DFBIA demonstrated the best agreement with FM and FFM derived from DXA. The limits of agreement suggest that at a population level the use of DFBIA is acceptable as an alternative to DXA for the prediction of total FM and FFM. The anthropometric results show that CMC demonstrates the best agreement with DXA-FFM and that MAC demonstrates the best agreement with DXA-FM. The results also suggest that in order to minimise errors in measurements related to changes in TBW, that the timing of serial measurements should be standardised.

CHAPTER 4: RESULTS

4.1 PATIENT CHARACTERISTICS

The HD population at the time of recruitment was 83 patients. 27/83 patients (33%) volunteered to take part in the exercise programme. 25/83 patients who met the study criteria and satisfied the physician screen were recruited to the intervention group of the study. Two patients were excluded at the point of physician screening, one secondary to cerebrovascular disease (CVA) and one secondary to a recent myocardial infarction (MI). An additional 13 patients who met the study criteria and satisfied the physician screening, but did not wish to exercise, agreed to act as non randomised controls (Figure 4.1).

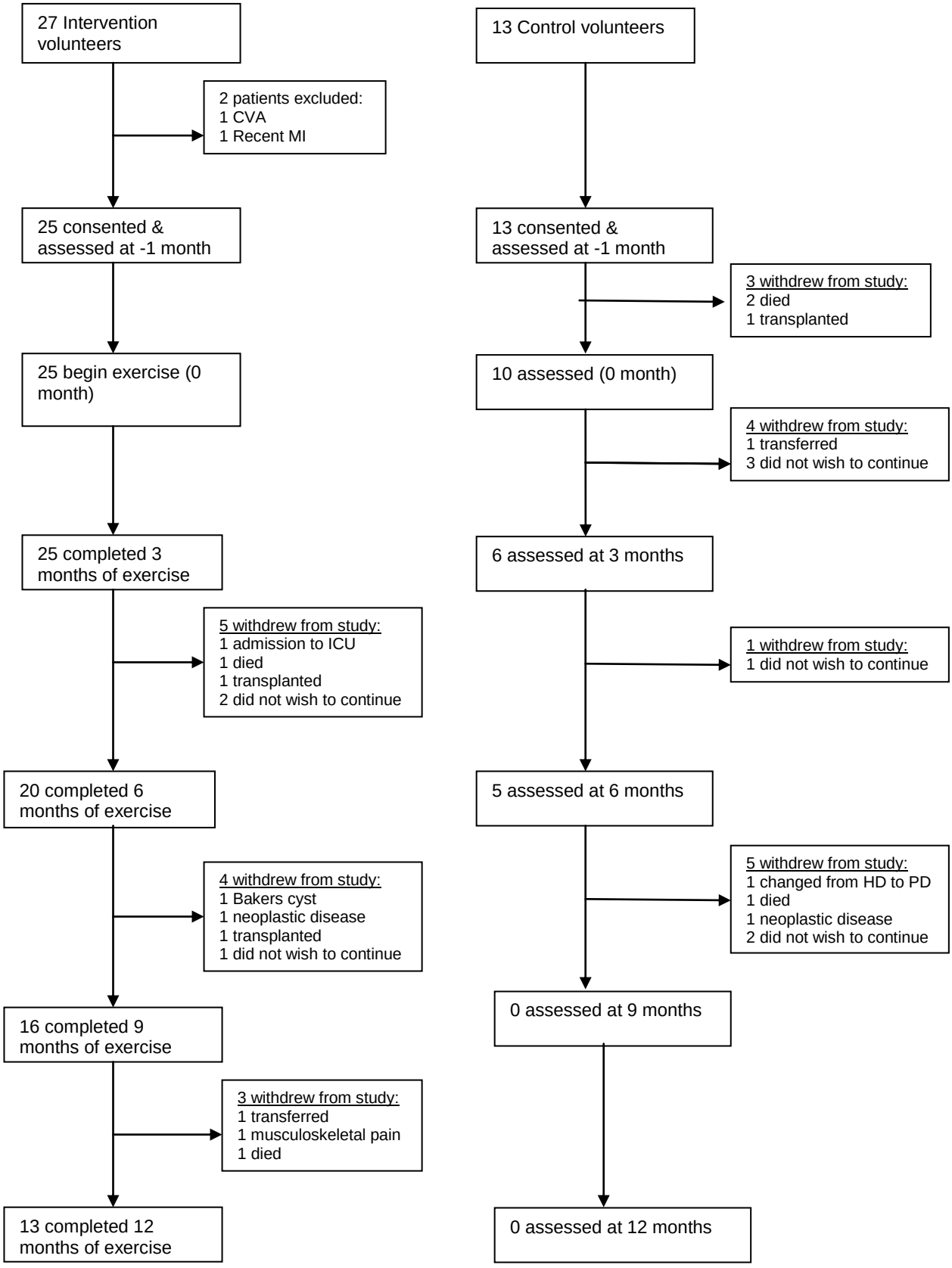
Patient characteristics at recruitment (- 1 month) are shown in Table 4.1. There were no significant differences in age, dialysis vintage or co-morbidity score between the intervention and control group.

Table 4.1: Patient characteristics at recruitment

	Intervention Group (n=25)	**Control Group** (n=13)
Gender	13M: 12F	9M: 4F
Age	56.0 ±11.4	60.8 ± 14.6
Dialysis vintage (months)	65.2 ± 99.0	36.9.± 9.6
EDTA Grouping		
1 (Primary Glomerulonephritis)	8 (32%)	3 (23%)
2 (Interstitial Nephropathies)	5 (20%)	1 (8%)
3 (Multisystem Diseases)	5 (20%)	6 (45%)
4 (Diabetes)	0 (0%)	2 (16%)
5 (Not Known and Other)	7 (28%)	1 (8%)
Co-morbidity score		
Low	11 (44%)	3 (23%)
Medium	10 (40%)	6 (46%)
High	4 (16%)	4 (31%)

(Values are presented as Mean ± SD). There were no significant differences between the groups

Figure 4.1: Patient recruitment and flow through study



Patient characteristics for functional status and quality of life are shown in Table 4.2. There was no significant difference between the two groups for handgrip strength and the time taken to complete the timed up and go test. There was, however, a significant difference in the number of sit to stands completed by the intervention group in comparison to the control group. In comparison to available normative data for healthy individuals both groups at recruitment demonstrated functional impairment. The number of sit to stand transitions completed within 60 seconds was 60% lower than those reported for healthy individuals 10 years older than the recruited population (Ritchie et al 2005). The time taken to complete the timed up and go test was slower than a normative mean time of 8.1 seconds for those aged 60-69 years (Bohannon 2006). Handgrip strength was approximately 70% of expected values for age matched healthy individuals (Kuh et al 2005)

At recruitment the mental component score (MCS) was not significantly different between the two groups and was not significantly different from the norm based score of 50 (Ware et al 2007). In both groups the physical component score (PCS) and domain scores for physical function (PF), role physical (RP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) were significantly lower than the norm based score of 50 ($p<0.03$). There were, however, no significant differences between the two groups. The bodily pain (BP) domain score was not significantly lower than the norm based score of 50 for the intervention group ($p=0.310$), but it was for the control group ($p=0.008$). The BP score was as a consequence significantly different between the two groups ($p=0.04$). The mental health (MH) domain score was significantly lower than the norm based score of 50 for the intervention group ($p=0.01$), but not the control group ($p=0.654$). However, the MH score was not significantly different between the two groups ($p=0.183$).

Table 4.2: Functional and quality of life characteristics at recruitment

	Intervention Group (n=25)	**Control Group** (n=13)
Functional		
Sit to stand (nos in 60 secs)	16.3 ± 5.7	10.8 ± 9.0*
Timed up & go (secs)	10.2 ± 3.2	12.9 ± 7.0
Handgrip strength (Kg)	25.3 ± 8.8	22.7 ± 8.1
Quality of Life		
SF36v2 component scores		
Physical Component Score (PCS)	38.1 ± 9.1	34 ± 10.1
Mental Component Score (MCS)	42.2 ± 13.2	44.7 ± 12.2
Domain Scores		
Physical Functioning (PF)	37.9 ± 10.4	33.4 ± 9.6
Role Physical (RP)	35.3 ± 11.8	37.5 ± 7.8
Bodily Pain (BP)	47.5 ± 12.1	40.1 ± 11.4*
General Health (GH)	36.2 ± 8.2	36.1 ± 10.5
Vitality (VT)	42.4 ± 11.7	38.4 ± 10.8
Social Functioning (SF)	36.5 ± 12.6	41.7 ± 11.6
Role Emotional (RE)	41.3 ± 12.3	36.7 ± 13.1
Mental Health (MH)	43.3 ± 12.1	48.5 ± 11.8

(Values are presented as Mean ± SD) With the exception of the sit to stand test (* p = 0.03, independent t-test) and bodily pain score (*p= 0.04, independent t-test) there were no significant differences between the groups.

Patient characteristics for nutritional status at recruitment are shown in Table 4.3. There were no significant differences between the groups. Both groups were considered over weight (BMI>25) in accordance with the classifications published by the World Health Oranisation (WHO 1995). The anthropometric results at recruitment demonstrate that in comparison to age matched normative data, the BMI was equal to the 50th percentile, mid arm circumference (MAC) and tricep skinfold (TSF), were equal to the 50th percentile, mid arm muscle circumference (MAMC) was between the 25th -50th percentile and the calf circumference (CC) was between the 15th-25th percentile (McDowell et al 2005).

Table 4.3: Nutritional characteristics at recruitment

	Intervention Group (n=25)	**Control Group** (n=13)
Height (metres)	1.67 ± 0.1	1.71 ± 0.1
Weight (kg)	73.7 ± 16.5	76. 0 ± 21.3
Body mass index (kg/m^2)	26.5 ± 5.4	25.6 ± 4.8
Midarm circumference (cm)	30.4 ± 4.9	30.2 ± 4.0
Tricep skinfold (mm)	18.1 ± 8.8	18.9 + 6.6
Midarm muscle circumference (cm)	24.8 ± 3.1	24.3 ± 3.5
Calf circumference (cm)	35.4 ± 4.2	35.3 ± 3.5
Calf skinfold (mm)	14.4 ± 8.2	15.8 ± 6.8
Calf muscle circumference (cm)	30.9 ± 3.6	30.3 ± 3.2
DFBIA-TBW (L)	34.5 ± 6.4	36.7 ± 9.5
DFBIA-FM (Kg)	26.0 ± 11.4	25.8 ± 10.6
DFBIA-FFM (Kg)	47.2 ± 8.7	50.2 ± 12.9
DFBIA-%FM	34.5 ± 8.6	33.1 ± 7.6
DFBIA-%FFM	65.5 ± 8.6	66.9 ± 7.6
DFBIA- ECW (L)	16.8 ± 2.6	17.5 ± 3.4
DFBIA-ICW (L)	17.7 ± 3.9	19.3 ± 6.1
DFBIA- ECW:ICW ratio	0.97 ± 0.1	0.94 ± 0.1
DFBIA-ECW:TBW ratio	0.49 ± 0	0.48 ± 0
PCR (g)	57.0 ± 17.7	61.8 ± 18.0
nPCR (normalised for ideal body wt -g/kg/IBW)	0.90 ± 0.3	0.90 ± 0.2

(Values are presented as Mean ± SD) There were no significant differences between the groups.

The clinical characteristics for clinical status at recruitment are shown in Table 4.4. There were no significant differences between the two groups. From a therapeutic target perspective, both groups met the national UK targets (Mactier 2007) set for pre dialysis serum potassium (between 3.5- 6.5mmol/l), albumin, corrected calcium (to be within the normal range), dialysis adequacy (eKt/v>1.2, URR>65%), haemoglobin (pre dialysis Hb of 11g/dl-12g/dl (or 10.5- 12.5)) and haematocrit (>33%). The target (1.1-1.8mmol/l) for pre dialysis serum phosphate was met by the control group, but not the intervention group. The target for pre dialysis blood pressure was met by the control group, but not the intervention group (140/90 mmHg). Both groups showed signs of low grade systemic inflammation (hsCRP >5mg/l).

Table 4.4: Clinical characteristics at recruitment

	Intervention Group (n=25)	**Control Group** (n=13)
Pre dialysis sodium (mmol/l)	139.0 ± 2.7	137.5 ± 2.4
Post dialysis sodium (mmol/l)	135.9 ± 2.2	135.7 ± 1.8
Pre dialysis potassium (mmol/l)	5.2 ± 0.8	5.1 ± 0.6
Post dialysis potassium (mmol/l)	3.7 ± 0.4	3.6 ± 0.5
Pre dialysis bicarbonate (mmol/l)	21.7 ± 2.5	22.1 ± 2.6
Post dialysis bicarbonate (mmol/l)	27.4 ± 2.6	28.0 ± 2.8
Pre dialysis urea (mmol/l)	22.8 ± 6.0	22.3 ± 4.9
Post dialysis urea (mmol/l)	7.7 ± 2.4	7.2 ± 2.3
Pre dialysis creatinine (µmols/l)	876 ± 207.4	734 ± 218.7
Post dialysis creatinine (µmols/l)	367 ± 366.9	293 ± 77.8
Pre dialysis phosphate (mmol/l)	1.84 ± 0.4	1.64 ± 0.4
Pre dialysis corrected calcium (mmol/l)	2.40± 0.2	2.42 ± 0.2
Pre dialysis albumin (g/l)	36.5 ± 2.9	37.8 ± 3.0
Pre hsC-reactive protein (mg/l)	14.4 ± 20.5	20.6 ± 14.5
Post hsC-reactive protein (mg/l)	15.0 ± 20.1	19.3 ± 15.0
eKt/v	1.28 ± 0.2	1.30 ± 0.2
URR (%)	66.2 ± 6.6	67.9 ± 5.4
Pre dialysis leptin (µg/l)	10.3 + 8.2	10.5 ± 11.6
Post dialysis leptin (µg/l)	7.9 ± 6.1	9.9 + 9.2
Pre dialysis systolic blood pressure (mmHg)	145.8 ± 27.2	138.5 ± 26.1
Pre dialysis diastolic blood pressure (mmHg)	78.8 ± 12.3	77.2 ± 13.7
Pre dialysis haemoglobin (g/dl)	11.5 ± 1.6	11.6 ± 1.6
Pre dialysis haematocrit (%)	34.3 ± 0.3	35.6 ± 0.0
ESA dose (mcg/week)	46.8 ± 31.4	50 ± 38.5
ESA/hct index	1.46 ± 1.1	1.52 ± 1.4
Total daily antihypertensive dose (mg)	127.1 ± 41.4	34.4 ± 13.7

(Values are presented as Mean ± SD). There were no significant differences between the groups.

4.2 WITHDRAWALS

The reasons for withdrawal are summarised in Table 4.5 and the pattern of withdrawal is shown in Figure 4.1. Over the course of the study, 12 patients (48%) withdrew or were withdrawn from the intervention group; five withdrew between three and six months (20%), a further four withdrew between six and nine months (36%) and a further three between nine and twelve months. Of the patients who withdrew from the intervention group, 6 had an initial comorbidity score of 1 (low risk), 5 had an initial comorbidity score of 2 (medium risk) and 1 had an initial comorbidiy score of 3 (high risk).13 patients (100%) in the control group withdrew or

were withdrawn over the course of the study; 3 withdrew between -1 month and 0 months, 4 withdrew between 0 months and 3 months, 1 withdrew between 3 months and 6 months and the rest withdrew between 6 months and 9 months.

Table 4.5: Reasons for withdrawal from study (n)

Intervention group	Control group
Death (2)	Death (3)
Diagnosis of neoplastic disease (1)	Diagnosis of neoplastic disease (1)
Transfer to another unit (1)	Transfer to another unit (1)
Renal Transplant (2)	Renal Transplant (1)
Did not wish to continue (3)	Did not wish to continue (6)
Admission to Intensive Care Unit (1)	Change from HD to PD (1)
Bakers cyst at back of knee (1)	
Musculoskeletal pain in knees (1)	

4.3 EXERCISE LOGS

The analysis of the exercise logs was hampered due to a number of missing or non-completion of logs by dialysis staff. Results are therefore based on complete exercise logs at each time point as follows: 19/25 logs at 3 months, 15/20 logs at 6 months, 11/16 logs at 9 months and 9/13 logs at 12 months.

The target for the intervention group was to complete three sessions of intradialytic exercise per week. The actual number of sessions undertaken by patients per week is shown in Figure 4.2. Although there was a reduction in the number of weekly sessions undertaken at 6 months, there were no significant differences over time for the weekly number of sessions undertaken ($p= 0.678$). Based on this information, the participation rate, expressed as a percentage of completed sessions versus possible sessions, was 82%.

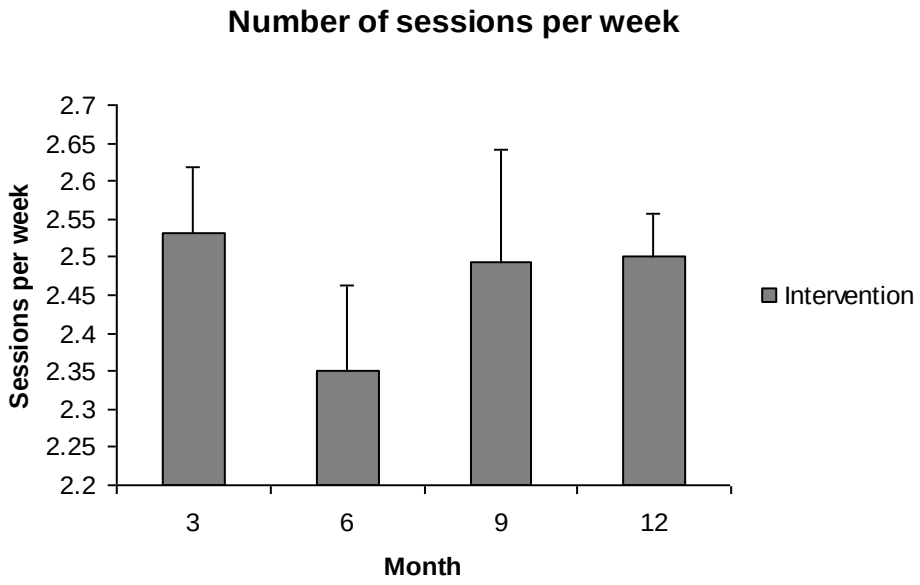


Figure 4.2: Number of intradialytic exercise sessions per week over time (mean ± SEM) (n=19 at 3 months, n= 15 at 6 months, n=11 at 9 months, n=9 at 12 months). RM ANOVA demonstrated no significant difference over time *F* (2.1, 14.5) = 0.411, p = 0.678.

The exercise protocol instructed patients to increase the duration of each exercise session from 3 minutes by 1 minute until 30 minutes was achieved. Figure 4.3 demonstrates that patients were able to significantly increase the duration of their sessions ($p < 0.001$) in keeping with the study protocol and were then able to maintain the duration of each exercise session as per the protocol.

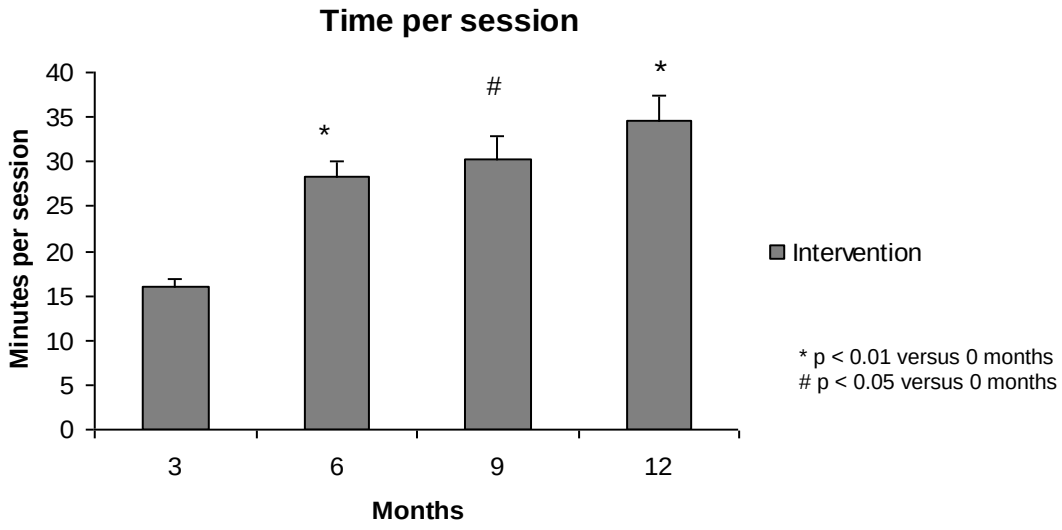


Figure 4.3: Minutes cycled per exercise session (mean ± SEM) (n=19 at 3 months, n= 15, at 6 months, n=11 at 9 months, n=9 at 12 month). RM ANOVA showed there was a significant increase in the duration of the sessions over time *F* (1.9, 13.2) =17.46, p <0.001.

It is however evident from Figure 4.2, that there were a number of occasions when patients missed exercise sessions. Where available and when documented the reasons, in order of commonality are given in Table 4.6.

Table 4.6: Summary of reasons for missed exercise sessions

Reason	Number of occasions
Patient didn't feel like it	89
Dialysis staff otherwise occupied/too busy to set up the bike	75
Fistula related or blood flow problems	61
Musculoskeletal pain (knees/back/foot)	42
Unwell (not specified)	27
Hypotension (pre or during first hour of HD)	21
Planned trip away	18
Infection	17
Headache	12
Patient working post HD	4
Cramp	4
GI upset	4
Problem with cycle ergometer	3
Fluid overload	2
Chest pain (unrelated to exercise)	1

In addition to being able to progressively increase and maintain time patients were able to progressively increase the level of resistance between 3, 9 and 9 months as per the protocol (Figure 4.4). However there was no significant increase in the level of resistance between 9 and 12 months, which was not in keeping with the protocol.

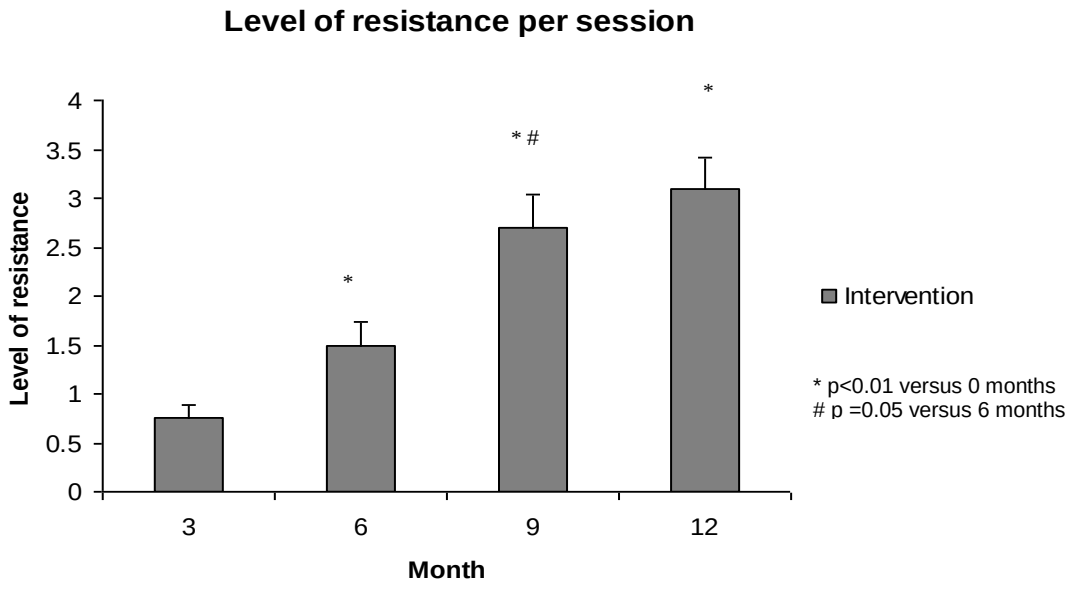


Figure 4.4: Level of resistance per exercise session (mean ± SEM) (n=19 at 3 months, n= 15 at 6 months, n=11 at 9 months, n=9 at 12 months). RM ANOVA showed there was a significant increase in resistance over time $F(1.4, 9.7) = 29.73$, $p < 0.001$.

4.4 Associations between levels of resistance and outcome measures

Associations between the different components of the exercise protocol (time, number of completed sessions and level of resistance) with other outcome measures were explored. No significant associations were found between time or the number of completed exercise sessions. However, significant associations were found between levels of resistance and other outcome measures. One of these was a significant negative association between the level of resistance and the time taken to complete the TUG at 3, 6, 9 and 12 months (Figure 4.5). The association was

observed to strengthen over time. This may imply that higher levels of resistance are equated to completing the TUG in less time.

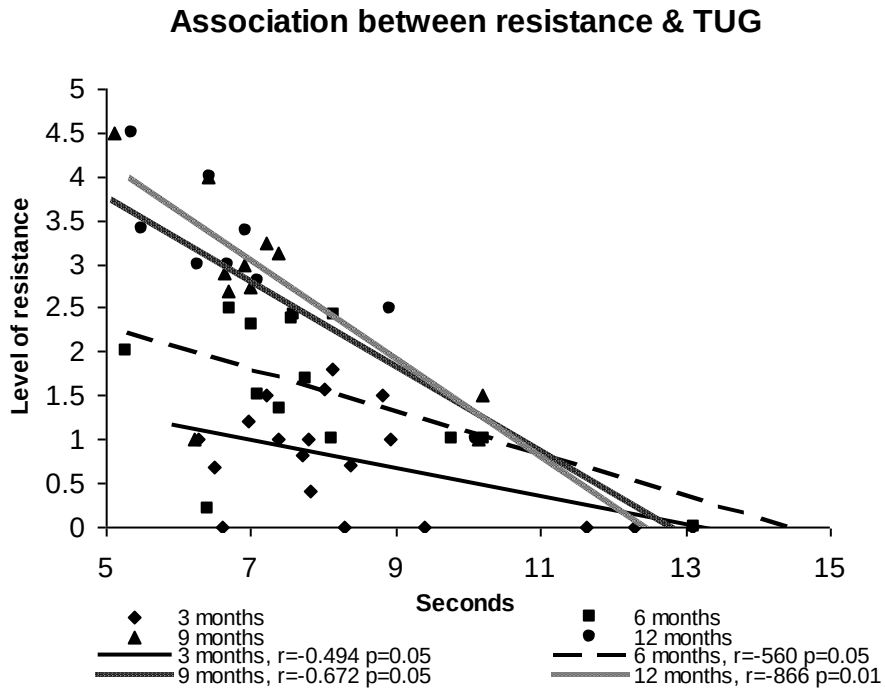


Figure 4.5: Association between the level of resistance and timed up and go test (TUG) at 3, 6, 9 and 12 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13).

A significant and positive association of moderate strength was found between levels of resistance and the number of sit to stands completed in 60 seconds at 3, 6 and 9 months (Figure 4.6). There was no significant association observed at 12 months. Such an association suggests that as levels of resistance increased was a corresponding increase in the number of sit to stand transitions patients could achieve in 60 seconds occurred. In addition, a significant and strong positive association was also found between levels of resistance and changes in handgrip strength at 3, 6 and 9 months. This association strengthened over time to the point of 9 months (Figure 4.7). This relationship would indicate that a higher level of resistance is associated with greater handgrip strength. No significant association was observed at 12 months.

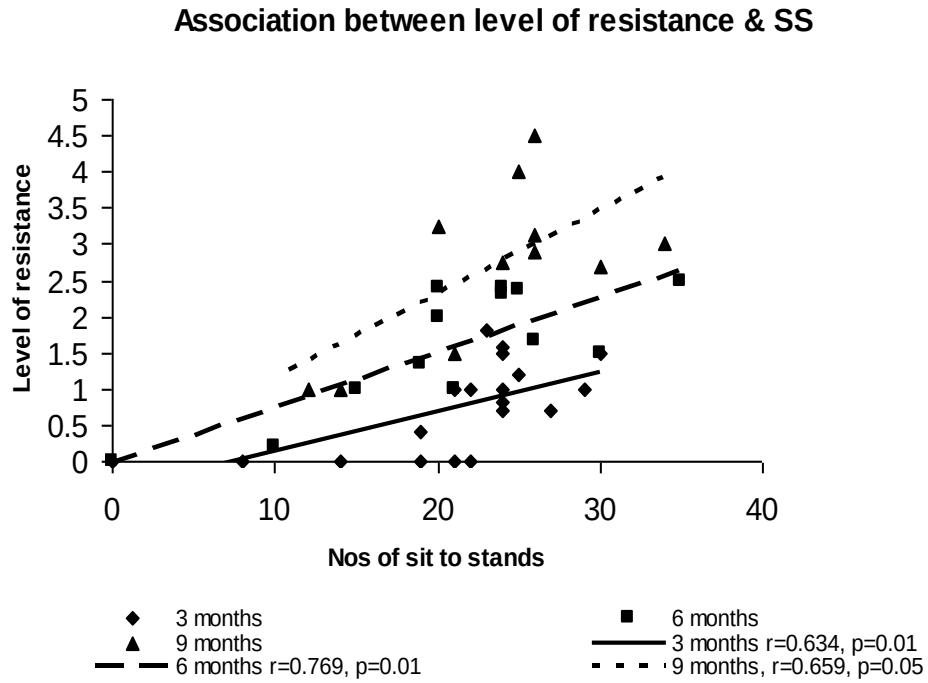


Figure 4.6: Association between the level of resistance and number of sit to stands (SS) in 60 seconds at 3, 6 and 9 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16).

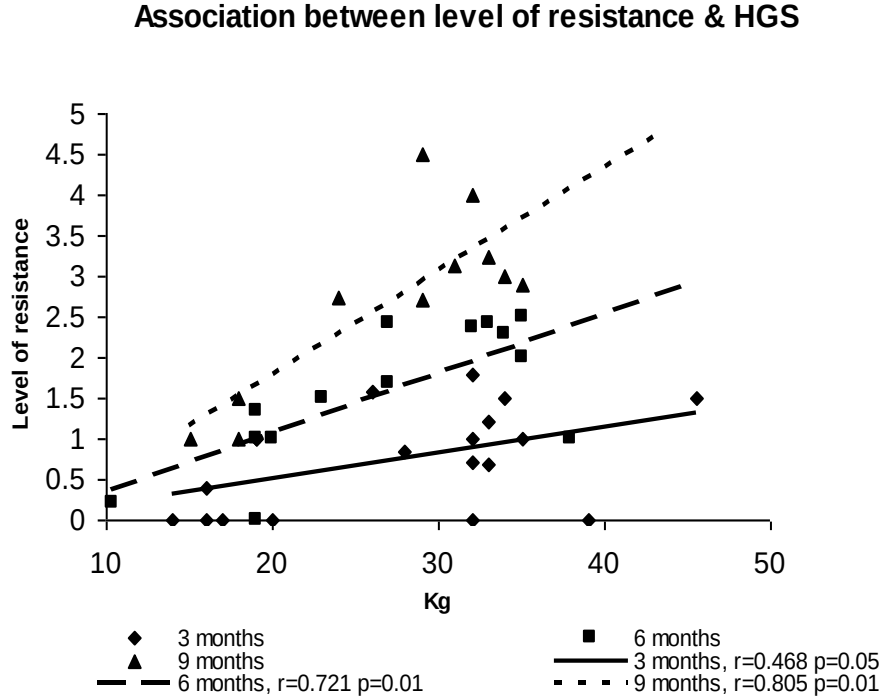


Figure 4.7: Association between the level of resistance and handgrip strength (HGS) at 3, 6 and 9 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16)

Finally, a significant positive association was found between the levels of resistance and calf muscle circumference (CMC) at 3, 6 and 9 months (Figure 4.8). No association was observed at 12 months. The relationship would suggest that higher levels of resistance are associated with a higher CMC.

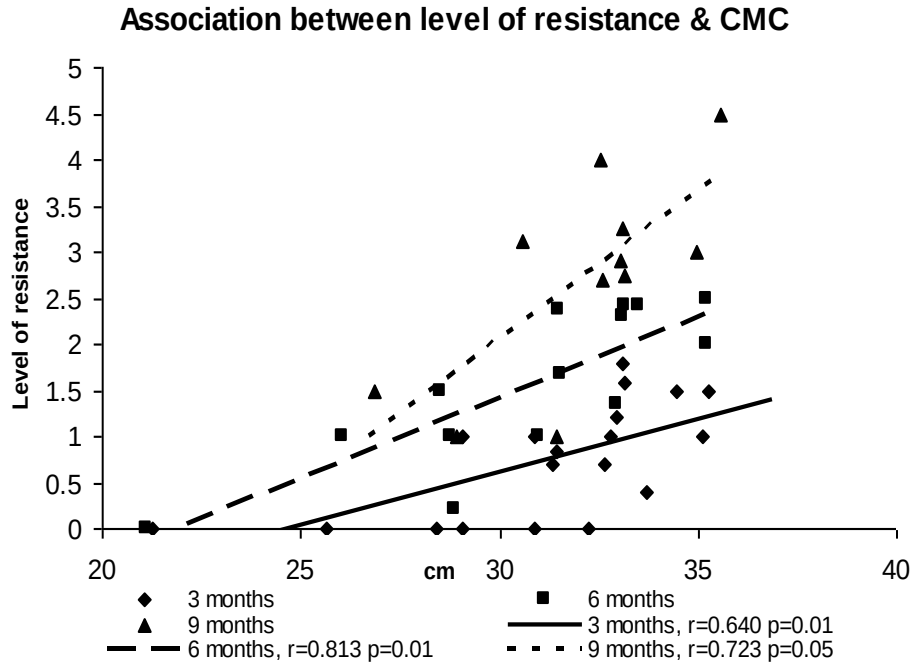


Figure 4.8: Association between the level of resistance and calf muscle circumference (CMC) at 3, 6 and 9 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16).

4.5 EFFECT OF EXERCISE ON FUNCTION

4.5.1 Sit to stand performance

In the intervention group there was a progressive and significant ($p < 0.001$) increase from 3 months onwards in the number of sit to stand transitions completed in 60 seconds. Over the 12 month period this translated to a 48% increase. Post hoc analysis showed no significant change between -1 month and 0 months; a significant increase between 0 months and 3 months which was then maintained between 3 and 6 months and another significant increase between 6 and 9 months which was then maintained between 9 and 12 months. While not significant, a downward trend ($p = 0.061$) in the number of sit to stands completed in 60 seconds was observed in the control group over the six month period (Figure 4.9)

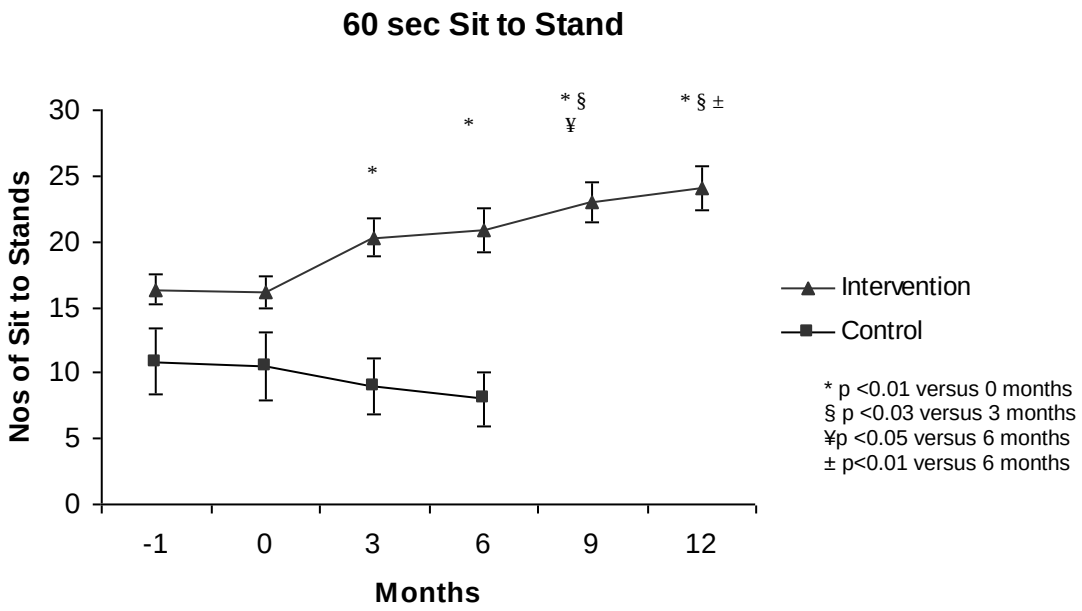


Figure 4.9: Number of sit to stand transitions completed within 60 seconds (mean ± SEM) for the intervention (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5). RM ANOVA shows there was a significant increase over time in the number of sit to stand transitions completed by the intervention group F (2.2, 26.9) = 26.52, $p < 0.001$.

4.5.2 Timed Up and Go performance

In the intervention group, a progressive and significant decrease in the time taken to complete the timed up and go (TUG) test was observed ($p < 0.001$) (Figure 4.10). Over the 12 month period this translated to a 25% decrease in the time taken to complete the test. Post hoc analysis showed there was no significant change between -1 month and 0 months and that a significant progressive decrease occurred at all time points there after. Although there was some variability noted (see Figure 4.10) in the time taken to complete the test in the control group, there was no significant change over the 6 month period ($p=0.640$).

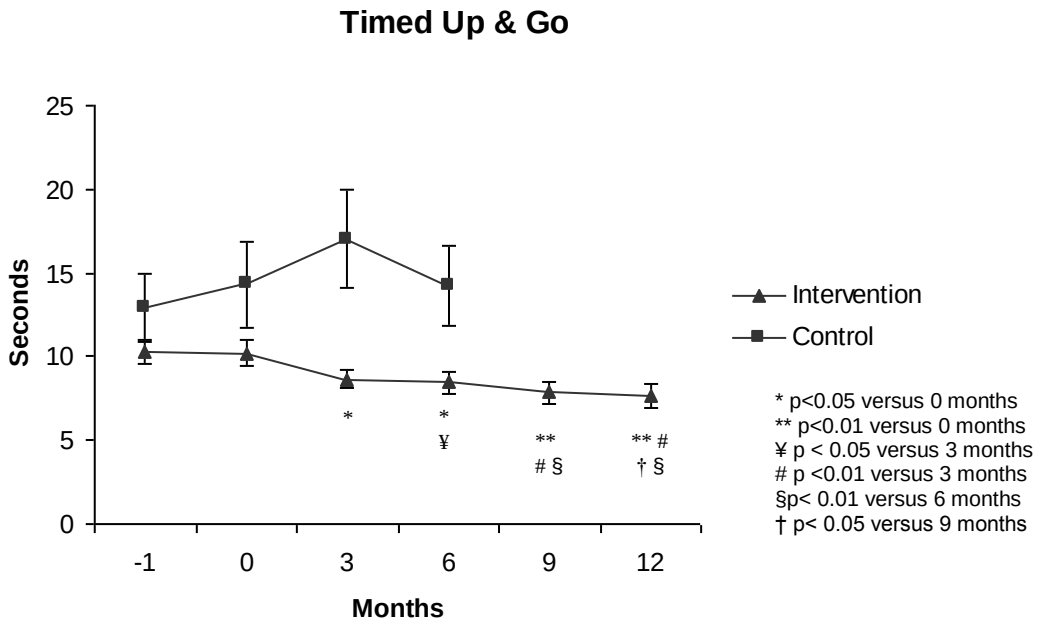


Figure 4.10: Seconds taken to complete the Timed up & Go test (mean ± SEM) for the intervention (at -1, 0 and 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5). RM ANOVA shows the time taken to complete the test significantly decreased in the intervention group F (1.9, 22.9) = 17.21, $p < 0.001$.

4.5.3 Handgrip strength

Over the 12 month period a progressive and significant increase in handgrip strength was observed in the intervention group ($p<0.001$) (Figure 4.11). Over the period of the study this amounted to a 25% increase in handgrip strength. Post hoc analysis revealed no significant difference between -1 months and 0 months; a significant increase between 0 months and 3 months. This significant increase was then maintained at 6 and 9 months. A further significant increase then occurred between 9 and 12 months. Although there was some variability in the results for the control group (see Figure 4.10), no significant change ($p=0.209$) in handgrip strength was observed over the 6 month period.

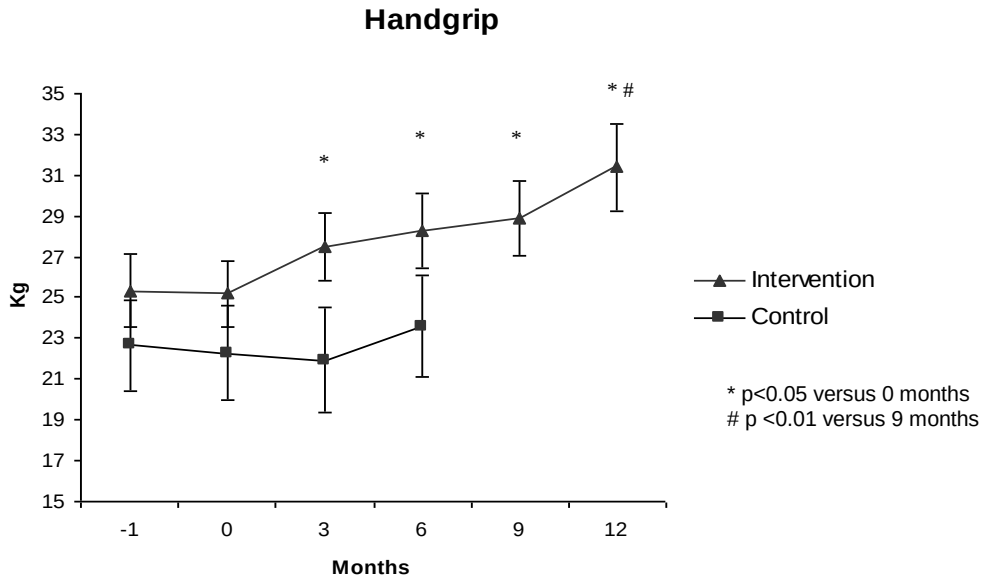


Figure 4.11: Handgrip strength results for the intervention (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5) over time (mean ± SEM). RM ANOVA shows there was a significant increase F (3.1, 36.9) = 9.10, $p<0.001$ in handgrip strength for the intervention group.

4.6: Associations between functional performance & other outcome measures

Associations between functional performance tests and nutritional and clinical outcome measures were explored. A significant negative association was observed between timed up and go and sit to stand performance at 3, 6, 9 and 12 months (Figure 4.12). The association suggests that as an increase in the number of sit to stand transitions occurred there was a decrease in the time taken to complete the timed up and go test.

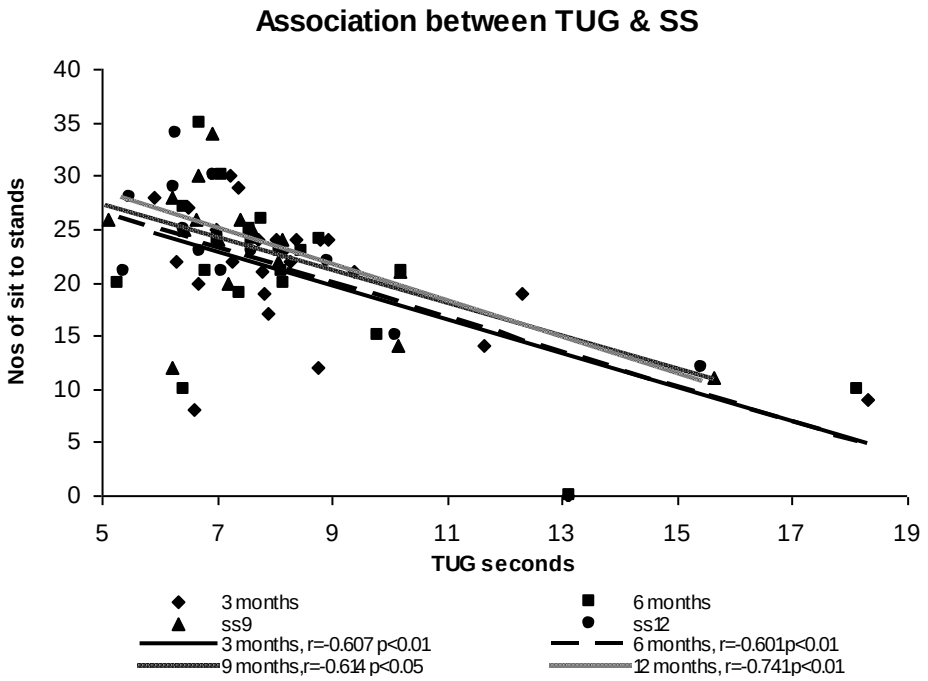


Figure 4.12: Association between the timed up and go (TUG) and sit to stand 60 second test (SS) at 3, 6, 9 and 12 months (n= 25 at 3 months, n=20 at 6 months, and n=16 at 9 months, n=13 at 12 months).

A significant positive association was also observed between sit to stand performance and handgrip strength (Figure 4.13). This association was observed at 3, 6 and 9 months. Such a relationship implies that as an increase in the number of

sit to stand transitions occurred there was a corresponding increase in handgrip strength. No significant association was observed at 12 months.

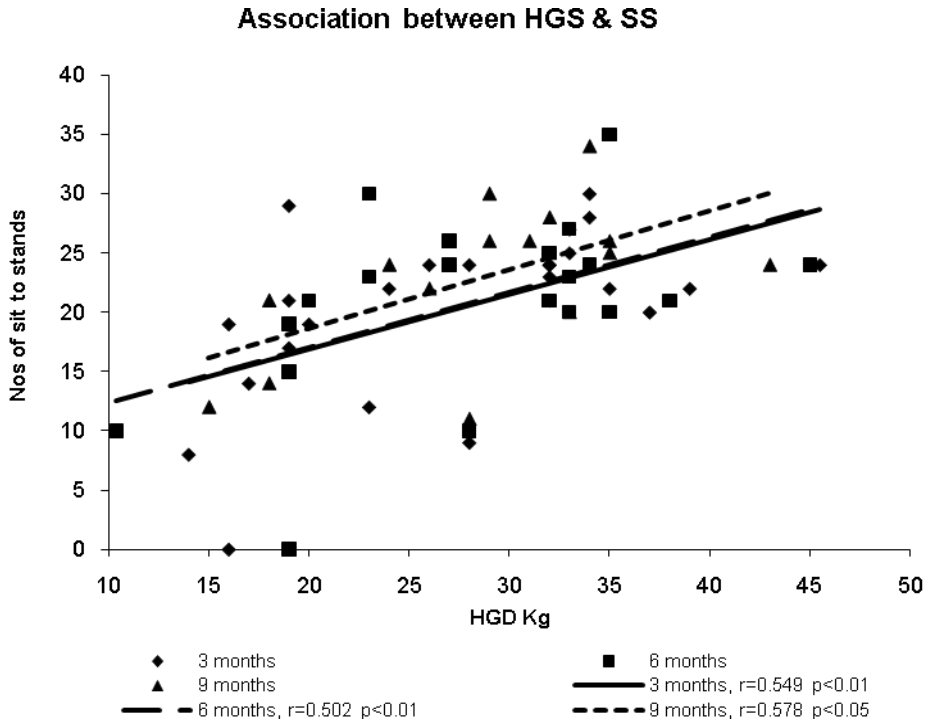


Figure 4.13: Association between handgrip strength (HGS) and sit to stand 60 seconds test at 3, 6 and 9 months (n= 25 at 3 months, n=20 at 6 months, n=16 at 9 months).

There was also a significant positive association observed between handgrip strength and calf muscle circumference at a 3, 6, 9 and 12 months (Figure 4.14). This relationship suggests that increased handgrip strength is equated to an increase in calf muscle circumference.

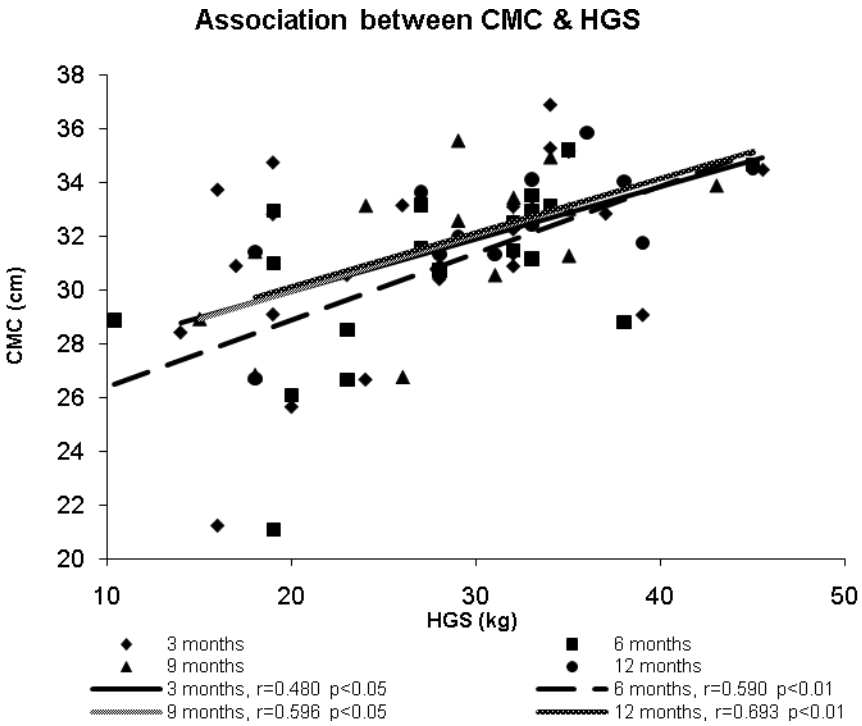


Figure 4.14: Association between calf muscle circumference (CMC) and handgrip (HGD) at 3, 6, 9 and 12 months (n= 25 at 3 months, n=20 at 6 months, and n=16 at 9 months, n=13 at 12 months).

In addition to the significant positive association between handgrip strength and calf muscle circumference a significant positive association was also observed between sit to stand performance and calf muscle circumference (Figure 4.15). This association was only significant at 3 and 6 months. This would imply that increases in sit to stand performance are associated with increases in calf muscle circumference up to the point of 6 months.

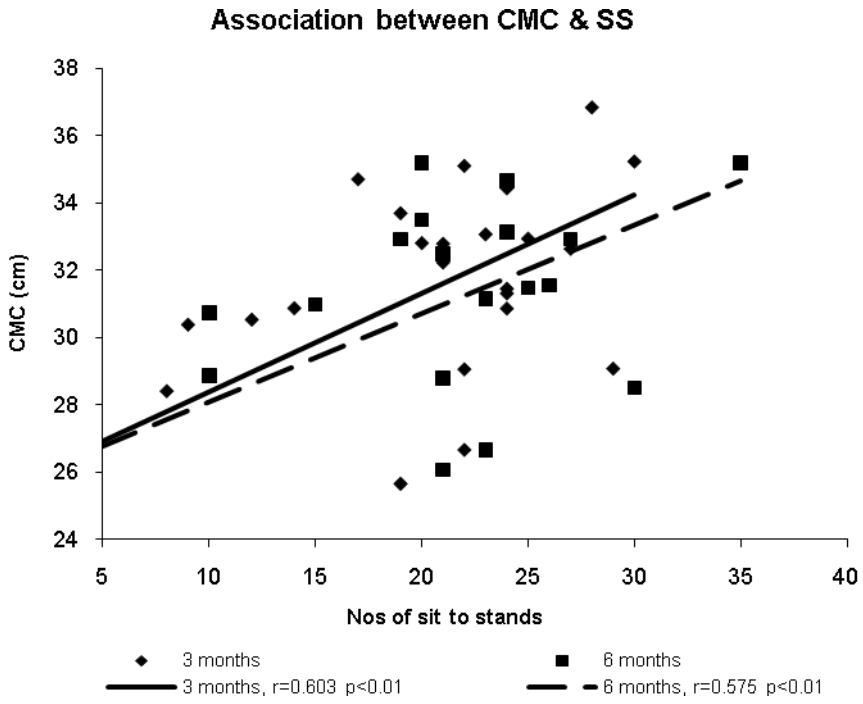


Figure 4.15: Association between calf muscle circumference (CMC) and number of sit to stand transitions (SS) (n= 25 at 3 months, n=20 at 6 months).

4.7: EFFECT OF EXERCISE ON QUALITY OF LIFE

4.7.1 Physical and mental component scores of SF36v2

In the intervention group a significant increase in the physical component score (PCS) was observed over the 12 month period (p = 0.007) (Figure 4.16). This change amounted to a 9.9 point increase. Post hoc analysis showed there was no significant difference between -1 month and 0 months. Whilst there was an increase observed at 3 months this did not reach statistical significance (p=0.059). Post hoc analysis shows the first significant increase in PCS occurred at 6 months which was maintained until a further significant increase occurred at 12 months. Although the results for the control group show some variability (see Figure 4.16) there was no significant change in PCS observed (p=0.555).

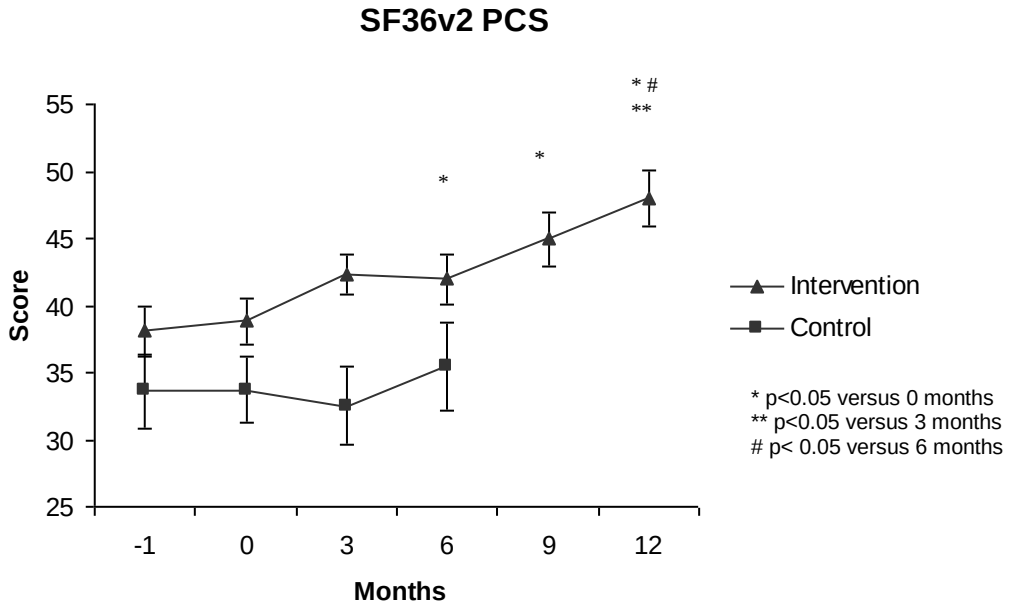


Figure 4.16: SF36v2 Physical Component Score (PCS) for the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5 (mean $\pm$ SEM). RM ANOVA shows there was a significant increase in PCS over time for the intervention group F (2.6, 29) = 5.13, p=0.007.

In contrast to the changes seen in the PCS component, there was no significant change over time for the mental component score (MCS) in the intervention (p =0.25) (42.2 $\pm$ 2.7 v 47.4 $\pm$ 2.7). This non-significant change was also mirrored in the control group (44.7 $\pm$ 3.4 v 45.6 $\pm$ 4.7) (p=0.33).

4.7.2: Domain scores of SF36v2

Significant increases in 5 out of the 8 domain scores, indicating improvements in perceived function and psychosocial well being, were observed in the intervention group over the 12 month period. The domains that improved significantly were: physical functioning (PF), role physical (RP), general health (GH), vitality (VT) and social functioning (SF). Trends towards improvement in bodily pain (BP) and mental health (MH) were also observed over time in the intervention group. The only

domain which remained static in the intervention group was the role emotional domain (RE). Conversely in the control group, there were no significant changes or trends observed in any of the eight domains at 6 months. Table 4.7 provides a summary of the changes seen in the SF36v2 domain scores for both the intervention and the control group.

Table 4.7 Summary of changes in quality of life (QOL)

Domain	**Intervention**				**Control**		
	-1 month n=25	**6 Months** n=20	**12 months** n=13	**p**	**-1 month** n=13	**6 months** n=5	**p**
PF	37.9 ± 10.4	40.2± 9.1	44.7± 9.2	0.017	33.4 ± 9.6	30.1± 6.9	0.340
RP	35.3 ± 11.8	40.5± 12.6	45.0+11.4	0.006	37.5 ± 7.8	38.8±10.6	0.412
BP	47.5 ± 12.1	48.6± 9.4	54.9± 7.6	0.090	40.1 ± 11.4	45.3±11.5	0.884
GH	36.2 ± 8.2	42.2± 9.0	45.9± 9.2	0.006	36.1 ± 10.5	36.2±11.2	0.521
VT	42.4 ± 11.7	49.0± 9.7	51.4±10.0	0.028	38.4 ± 10.8	42.1± 8.1	0.786
SF	36.5 ± 12.6	44.0± 9.4	45.5±10.1	0.021	41.7 ± 11.6	40.5±13.3	0.466
RE	41.3 ± 12.3	42.9±11.4	43.9±12.1	0.296	36.7 ± 13.1	38.0±15.0	0.499
MH	43.3 ± 12.1	48.0± 9.4	48.9±10.5	0.082	48.5 ± 11.8	47.2± 9.7	0.343

Results are presented as mean ± SD

Figure 4.17 shows the changes over time for the physical function (PF) domain score of the SF36v2. A significant improvement in the PF domain score was observed in the intervention group (p =0.017). Post hoc analysis showed no significant difference between -1 month and 0 months. It also showed that a significant change first occurred at 3 months. While subsequent improvements in the PF score were observed, these were not statistically significant. Although the scores in the control group appear to be decreasing there was no significant change over time (p=0.340).

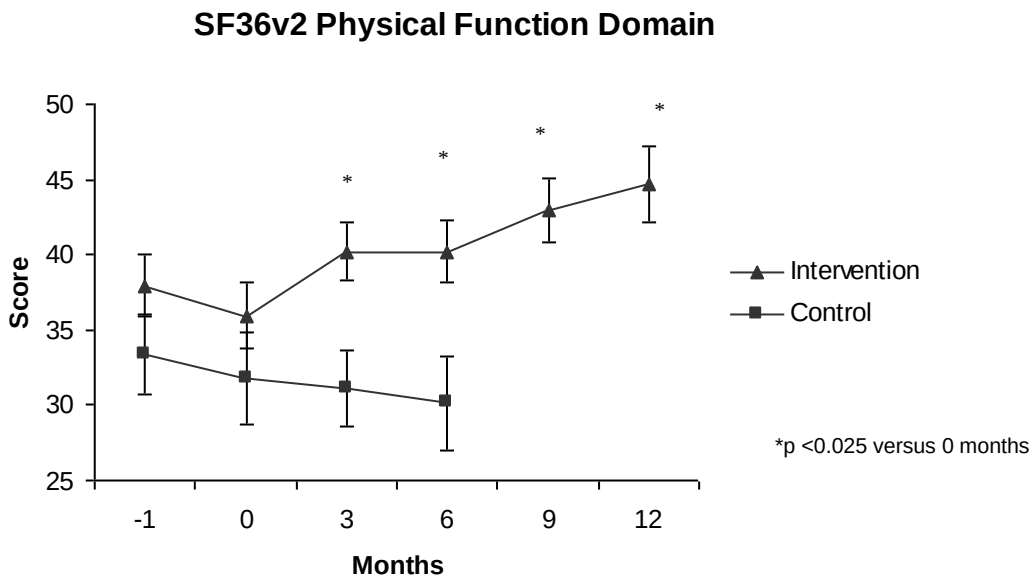


Figure 4.17: SF36v2 Physical function (PF) domain score for intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5) (mean ± SEM). RM ANOVA shows the change over time was significant for the intervention group F (2.3, 28) = 4.45, p = 0.017.

Figure 4.18 shows the changes over time for the role physical (RP) domain score of the SF36v2. A significant improvement in the RP domain score was observed in the intervention group (p =0.006). Post hoc analysis showed no significant difference between -1 month and 0 months. It also showed that a significant change occurred at 3 months which was maintained at 6 months. While subsequent improvements in the PF score were observed at 9 and 12 months, these were not statistically significant. Although the pattern of change in the control group up to 6 months appears to mirror that if the intervention group, there was no significant difference observed over time for the control group (p=0.412).

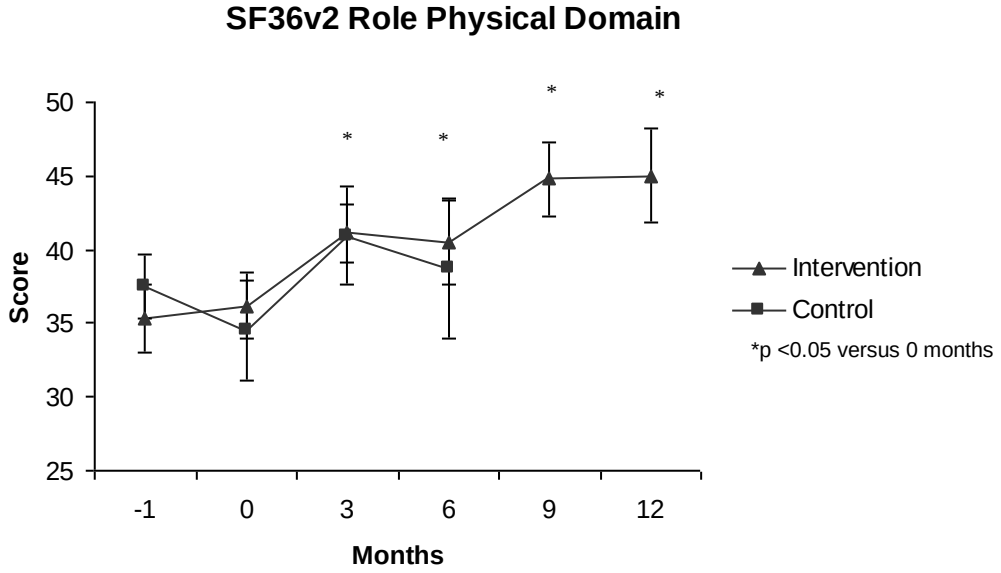


Figure 4.18: SF36v2 Role physical (RP) domain scores (mean ± SEM) for the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13. and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5) RM ANOVA shows the change over time was significant for the intervention group F (2.5, 29.6) =5.46, p = 0.006.

Figure 4.19 shows the changes over time for the general health domain score of the SF36v2. A significant and progressive improvement in the GH domain score was observed in the intervention group (p =0.006). Post hoc analysis showed no significant difference between -1 month and 0 months and showed a significant change in GH only at 12 months. Although there was some variability noted over time in the control group (see Figure 4.18), there was no significant difference over time (p=0.512).

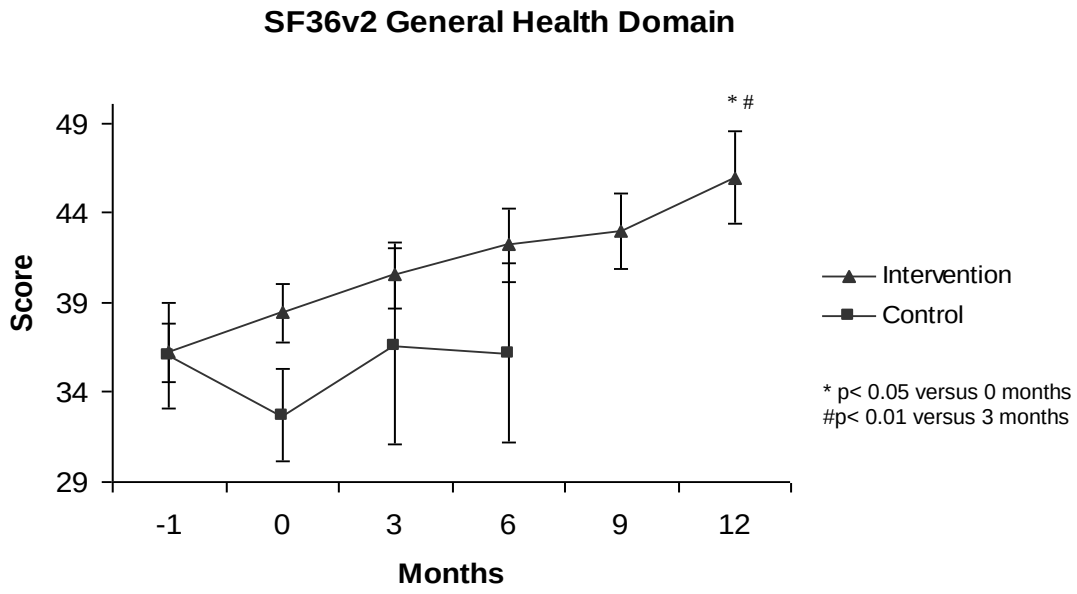


Figure 4.19: SF36v2 General health (GH) domain scores (mean ± SEM) for the intervention group (at -1, 0 and 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13. and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5). RM ANOVA shows the change in GH score was significant over time for the intervention group *F* (3.1, 37.8) =4.70, p=0.006.

Figure 4.20 shows the changes ove r time for the social functioning (SF) domain score of the SF36v2. A significant and progressive improvement in the SF domain score was observed in the intervention group (p=0.021). Post hoc analysis showed no significant difference between -1 month and 0 months and showed a significant change in SF did not occur until 12 months. Although the pattern of change in the control group up to 6 months appears to mirror that if the intervention group, no significant difference was observed (p=0.466).

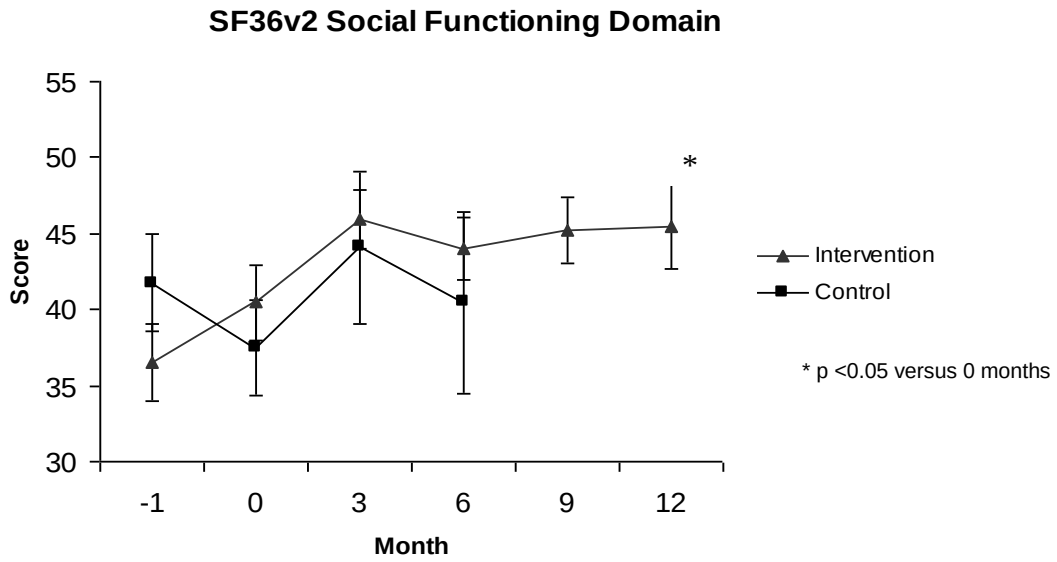


Figure 4.20: SF36v2 Social Functioning (SF) domain scores (mean ± SEM) for the intervention group (at -1, 0 and 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5. RM ANOVA shows the change over time in SF score was significant for the intervention group F (2.7, 31.9) = 3.89, p = 0.021.

Figure 4.21 demonstrates the changes over time for the vitality domain (VT) score of the SF36v2. A significant and progressive improvement in the VT domain score was seen in the intervention group (p=0.021). Post hoc analysis showed no significant difference between -1 month and 0 months and showed that a significant change in VT did not occur until 9 months which was then maintained at 12 months. While there was some variability in the control group scores (see Figure 4.21), there was no significant change over time (p=0.786).

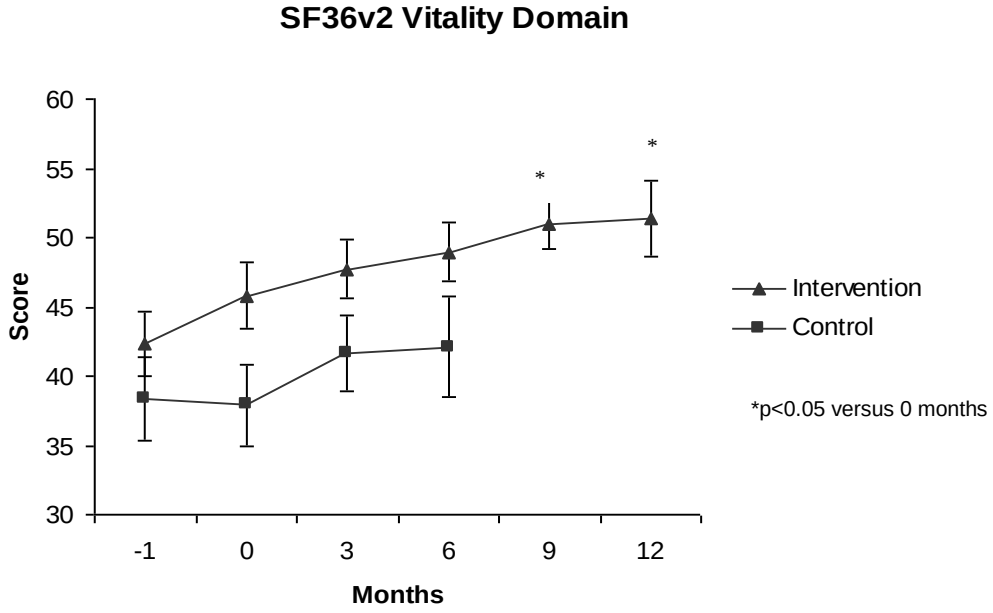


Figure 4.21: SF36v2 Vitality (VT) domain scores (mean ± SEM) for the intervention (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13.and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5). RM ANOVA shows the change in VT score was significant over time for the intervention group *F* (3.8, 39.2) =3.27, p = 0.028.

Few associations between the changes in QOL and other outcome measures were found. An association between VT and CMC was observed at 3, 6 and 9 months, but not 12 months (Figure 4.22). Such an association could suggest that as CMC increased there was a corresponding increase in perceived vitality. There was also a significant negative association between PF and pre dialysis hsCRP at 3 and 6 months (Figure 4.22) and a significant negative association between the PCS score and pre hsCRP at 6 months (r=-0.447, p=0.05). Such associations may imply that higher values of systemic inflammation negatively affect perceived levels of physical functioning.

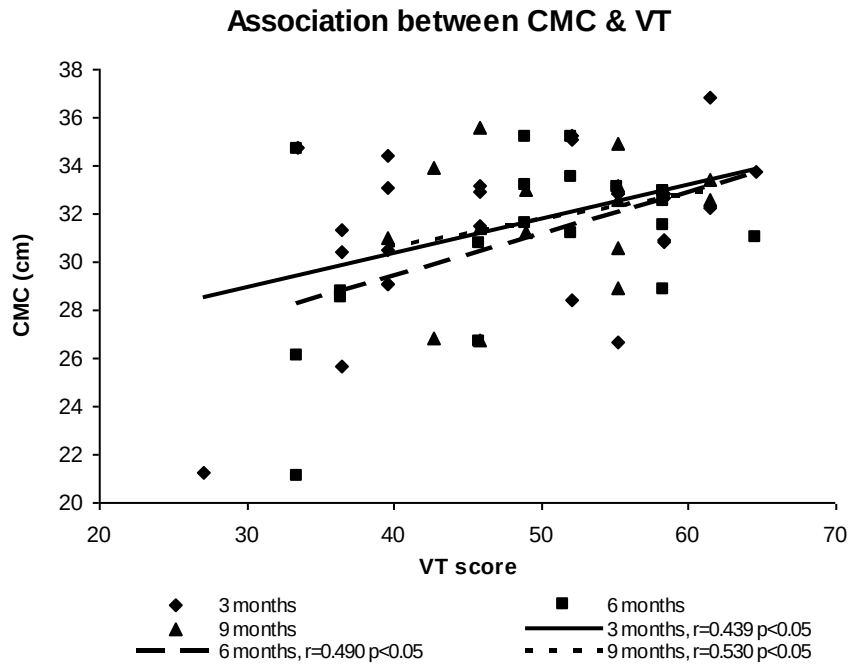


Figure 4.22: Association between the vitality domain (VT) and calf muscle circumference (CMC) at 3, 6 and 9 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13).

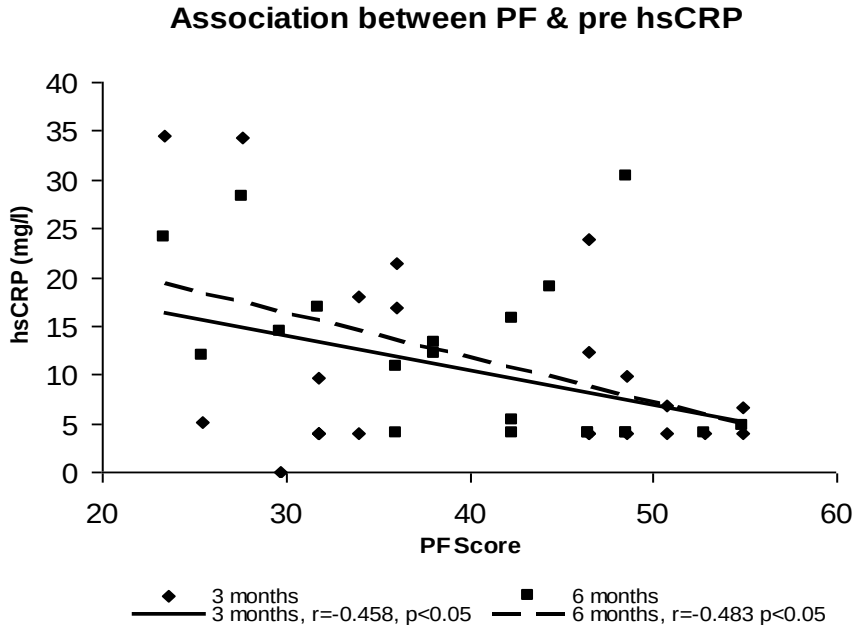


Figure 4.23: Association between the physical function domain and pre hsCRP at 3 and 6 months (at 3 months n= 25, at 6 months n=20).

4.8: EFFECT OF EXERCISE ON NUTRITIONAL STATUS

4.8.1: Anthropometry

A summary of the results for changes in body weight, BMI, limb circumferences and skinfolds are shown in Table 4.8. Body weight, BMI, MAC, CC did not change significantly overtime in either the intervention or the control group.

Table 4.8: Summary of changes in anthropometry

	Intervention				**Control**		
	-1 month (n=25)	**6months** (n=20)	**12 months** (n=13)	**p**	**-1 month** (n=13)	**6 months** (n=5)	**p**
Weight (kg)	73.7±16.5	71.8±15.4	77.7+12.0	0.713	76.0±21.3	82.8±18.5	0.645
BMI (kg/m^2)	26.5± 5.4	25.9± 4.8	27.5± 3.8	0.662	25.6± 4.8	30.6±0.13	0.529
MAC (cm)	30.4± 4.9	30.4± 4.9	32.1± 3.8	0.513	30.2± 4.0	31.0± 5.1	0.222
TSF(mm)	18.1± 8.8	16.5± 6.8	16.0± 5.6	0.094	18.9± 6.6	19.3± 6.2	0.317
MAMC (cm)	24.8± 3.1	25.2± 3.5	27.0± 2.8	0.004	24.3± 3.5	24.9± 4.3	0.406
CC (cm)	35.4± 4.2	35.1± 3.9	36.4± 2.2	0.380	35.3± 3.5	36.4± 3.5	0.215
CSF (mm)	14.4± 8.2	13.2± 7.3	12.7± 6.5	0.017	15.8± 6.8	15.8± 5.5	0.509
CMC (cm)	30.9± 3.6	31.4± 3.4	32.4± 2.2	0.001	30.3± 3.2	31.4± 3.3	0.438

Results are presented as mean ± SD

A significant increase in mid arm muscle circumference (MAMC) did occur over time in the intervention group (p = 0.004). Post hoc analysis showed there was no significant difference between -1 month and 0 months. It also showed that the first significant increase occurred at 6 months and although further increases did occur at 9 and 12 months these were not significant. There was no significant change observed over time in the control group (p =0.406) (Figure 4.24).

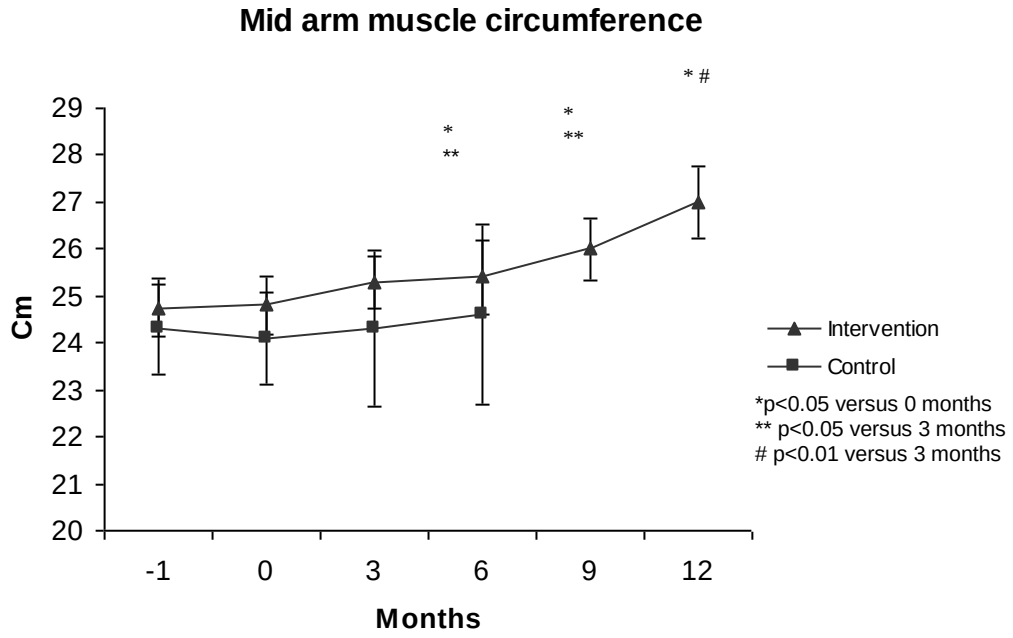


Figure 4.24: Mid arm muscle circumference (MAMC) over time (mean ± SEM) for the intervention group (At -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13).and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5). RM ANOVA shows the change over time in MAMC is significant for the intervention group F (2.7, 32.4) =5.58, p = 0.004.

A significant increase in calf muscle circumference was observed over time in the intervention group (p= 0.001). Post hoc analysis showed there was no significant difference between -1 month and 0 months and that the first significant increase in CMC was at 3 months. A further significant increase then occurred at 12 months. There was no significant change in the CMC over time for the control group (p=0.438). It should be noted that two patients in the control group had visual signs of ankle oedema at 3 and 6 months (Figure 4.25).

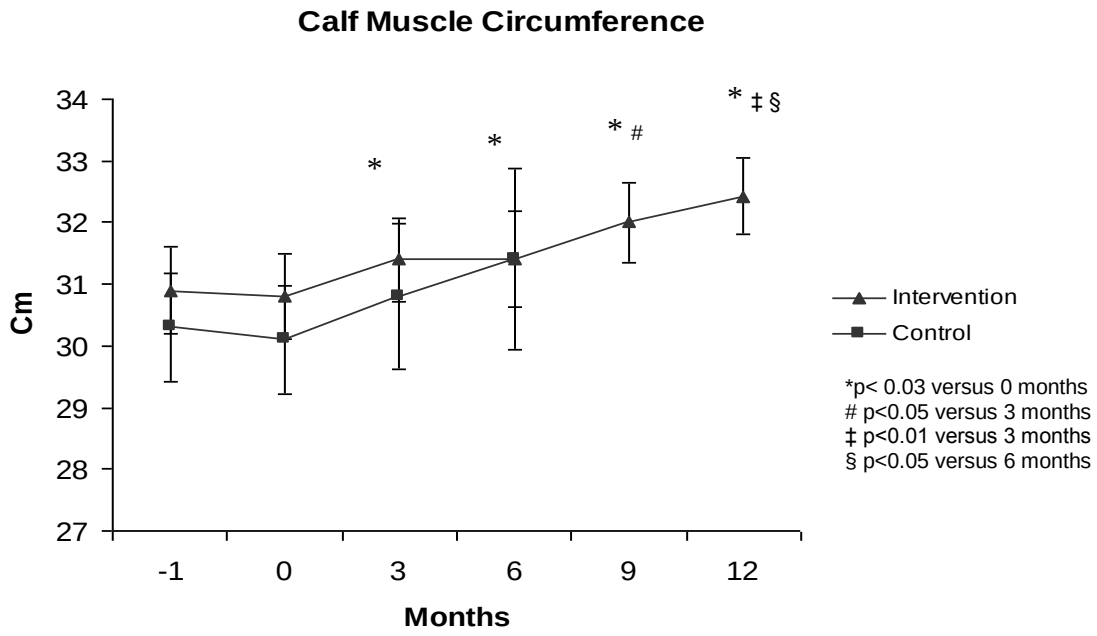


Figure 4.25: Calf muscle circumference (CMC) over time for the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5 (mean $\pm$ SEM). RM ANOVA shows the change in CMC over time is significant for the intervention group F (2.0, 23.7) = 9.39, p =0.001.

In contrast to the increase observed for CMC, a significant and progressive decrease in calf skinfold was observed in the intervention group (p=0.017) (Figure 4.26). Although a progressive decrease from 3 months to 6 months was observed, post hoc analysis showed this was not significant. The change at 9 months was, however, significantly different from 3 months. There was another small decrease at 12 months observed but post hoc analysis revealed this to be a non-significant decrease. In comparison there was no significant difference in calf skinfold observed over time for the control group (p= 0.509).

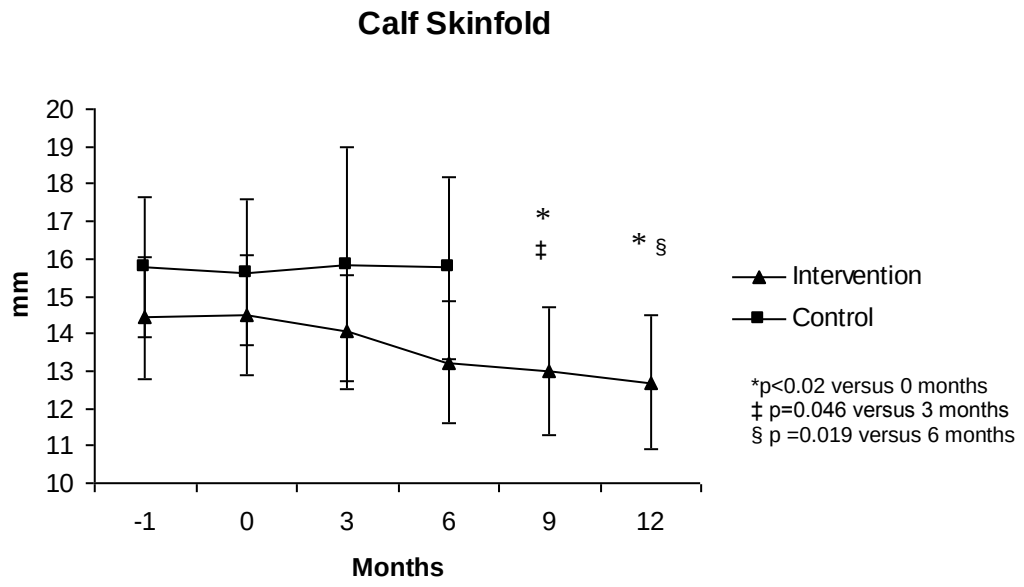


Figure 4.26: Calf skinfold (CSF) over time in the intervention (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5) (mean ± SEM). RM ANOVA shows the change in CSF over time is significant for the intervention group F (2.1, 25.3) = 4.70, p = 0.017.

Associations between CMC, MAMC and CSF and other outcome measures were also examined. No significant associations were found for MAMC or CSF. As previously shown significant associations were found between CMC, handgrip, sit to stand performance and the VT domain. In addition a significant positive association of moderate strength was found between CMC and haemoglobin (Figure 4.27). The association between haemoglobin and CMC was seen at all time points. Such a relationship would suggest that increases in CMC are associated with increases in haemoglobin.

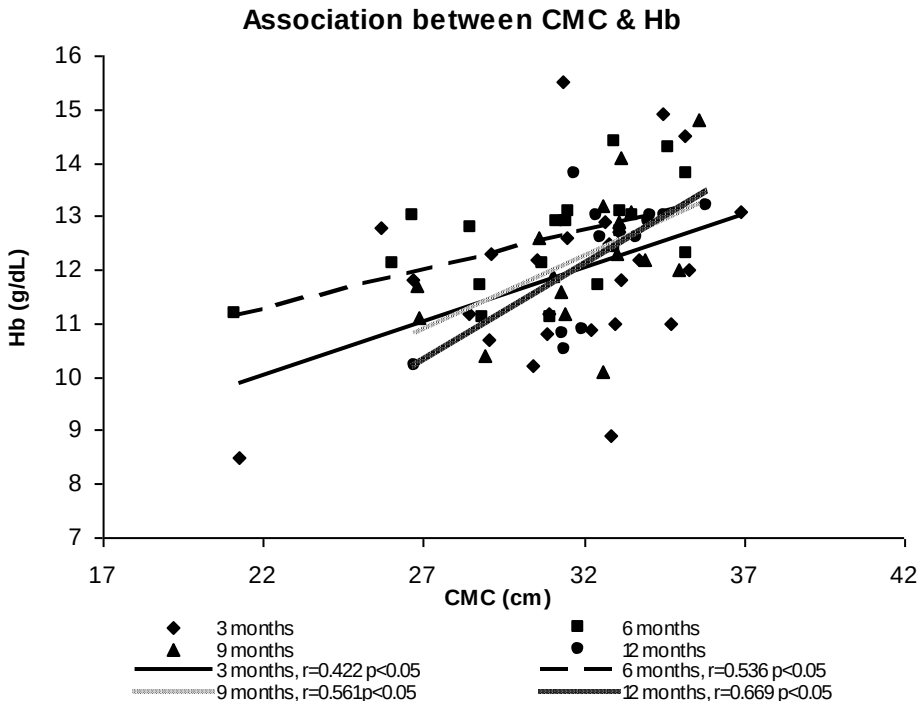


Figure 4.27: Association between calf muscle circumference (CMC) and haemoglobin (Hb) level at 3, 6, 9 and 12 months (at 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13).

4.8.2: Bioelectrical impedance analysis

A summary of the DFBIA results are shown in Table 4.9. In comparison with published percentiles for the general population, the recruited population's total FFM was comparable to the 25th-50th percentile and FM was comparable to the 75th-90th percentile (Kyle et al 2001). The results at recruitment show that in the post dialysis phase when reductions in total body water (TBW) have inevitably occured an expansion of the ECW compartment appears to remain (ECW: TBW, ECW: ICW).

In both groups, there were no significant changes in total body FM, FFM, TBW, ECW or ICW over time. Likewise no significant changes were observed in %FM, %FFM, %TBW, %ECW and the ECW: ICW, ECW: TBW ratios.

Table 4.9: Summary of changes in body composition measured by DFBIA

	Intervention				**Control**		
	-1 months n=25	**6 months** n=20	**12 months** n=13	**p**	**-1 months** n=13	**6 months** n=5	**p**
FFM (kg)	47.2 ± 8.8	47.5 + 8.6	49.8 ± 7.3	0.459	50.2 ± 12.9	51.6 ± 9.9	0.395
FM (kg)	26.0 ± 11.3	25.0 + 10.3	27.9 ± 9.1	0.301	25.8 ± 10.6	31.2 ± 9.3	0.417
% FFM	65.5 ± 8.6	66.5 + 8.1	65.0 ± 7.4	0.282	66.9 ± 7.6	63.4 ± 4.5	0.752
% FM	34.5 ± 8.6	33.5 + 8.1	35.5 ± 7.4	0.284	33.1 ± 7.6	37.4 ± 3.7	0.278
TBW (L)	34.5 ± 6.4	34.8 + 6.3	36.4 ± 5.3	0.458	36.7 ± 9.5	37.8 ± 7.3	0.397
%TBW	47.9 ± 6.3	48.7 ± 5.9	47.2 ± 5.4	0.282	48.9 ± 5.6	46.0 ± 2.8	0.834
ECW (L)	16.8 ± 2.6	16.9 + 2.6	17.5 ± 2.1	0.449	17.5 ± 3.4	19.8 ± 4.5	0.479
% ECW	23.6 ± 3.6	23.9 ± 3.4	22.7 ± 2.5	0.383	23.6 ± 3.1	24.1 ± 2.7	0.813
ICW (L)	17.7 ± 3.9	17.8 + 3.8	19.0 ± 3.3	0.569	19.3 ± 6.1	18.0 ± 4.2	0.395
ECW:ICW (L)	0.97 ± 0.1	0.97 + 0.1	0.93 ± 0.1	0.609	0.94 ± 0.1	1.13 ± 0.26	0.420
ECW:TBW (L)	0.49 ± 0.0	0.49 ± 0.0	0.48 ± 0.0	0.609	0.48 ± 0.0	0.48 ± 0.6	0.775

Results are presented as mean ± SD

4.8.3 Appetite and dietary intake

As indicated by the results presented in Table 4.10, there were no significant changes over time for pre dialysis or post dialysis ratings of hunger, satiety, fullness and prospective consumption (desire) in the intervention group or the control group.

Results from the diet diaries are based on daily intakes for the interdialytic period minus any consumption during the intradialytic period. Results for the intervention group are based on 18/25 patients who returned food diaries at -1 month, 19/25 at baseline, 17/25 at 3 months, 9/20 at 6 months, 8/16 at 9 months and 5/13 at 12 months. The results indicated no significant changes in interdialytic intakes of energy (1590 $\pm$ 106.4kcal/day v 1490 $\pm$ 94.5kcal/day, p=0.288) or macronutrient intakes of carbohydrate (190.0 + 14.6g/day v 175.7 $\pm$ 22.0g/day, p=0.367), fat (67.7 $\pm$ 5.0g/day v 69.2 $\pm$ 5.2g/day, p=0.332) or protein (66.8 $\pm$ 8.6g/day v 67.8 $\pm$ 11.4g/day, p=0.412) in the intervention group over time. Although seven patients in the control group returned food diaries at -1 month and baseline, subsequently only two patients returned food diaries at 3 months and 1 at 6 months. Therefore meaningful comparisons over time for the control group were not possible.

4.8.4 Protein catabolic rate (PCR) derived from urea kinetics

The PCR for the intervention group did not change significantly over the 12 month period (57.0 $\pm$ 3.5g v 63.7 $\pm$ 6.5g, p=0.436) nor did the nPCR (0.90 $\pm$ 0.1g/kg/IBW v 0.99 $\pm$ 0.1g, p=0.429). There was also no significant change in PCR (61.8 $\pm$ 5.0g v 63.5 $\pm$ 3.5g, p=0.253) or nPCR (0.90 $\pm$ 0.1g v 0.91 $\pm$ 0.1g, p=0.277) in the control group over the 6 month period.

Table 4.10: Summary of changes in pre and post dialysis appetite measured by visual analogue scale

(mm)	Intervention				Control		
	-1 months n=25	**6 months** n=20	**12 months** n=13	**p**	**-1 months** n=13	**6 months** n=5	**p**
Pre-hunger	46.7 ± 25.7	44.7 ± 28.2	47.2 ± 27.9	0.799	26.5 ± 22.2	20.0 ± 14.4	0.544
Pre-fullness	43.0 ± 29.6	41.6 ± 20.9	51.9 ± 19.1	0.913	51.7 ± 29.5	49.0 ± 17.6	0.402
Pre-satiety	41.4 ± 26.9	40.9 ± 25.9	43.5 ± 26.4	0.794	28.7 ± 20.3	28.5 ± 19.1	0.450
Pre-desire	46.6 ± 28.6	44.6 ± 30.4	52.2 ± 28.3	0.446	30.7 ± 24.6	26.7 ± 9.2	0.393
Post-hunger	52.4 ± 23.7	59.3 ± 23.4	62.2 ± 31.5	0.550	24.5 ± 19.8	29.0 ± 3.5	0.081
Post-fullness	41.3 ± 24.4	29.0 ± 19.5	39.7 ± 29.8	0.388	54.8 ± 28.9	44.8 ± 5.7	0.090
Post-satiety	54.2 ± 25.6	60.8 ± 18.0	59.1 ± 31.5	0.587	31.1 ± 14.0	30.7 ± 9.0	0.436
Post-desire	55.7 ± 31.7	58.5 ± 23.7	60.5 ± 28.8	0.473	28.4 ± 19.4	33.7 ± 8.1	0.151

Results are presented as mean ± SD

4.9 EFFECT OF EXERCISE ON CLINICAL STATUS

4.9.1 Dialysis adequacy

In the intervention group, there was no significant change over time for eKt/v (1.28 ± 0.4 v 1.35 ± 0.2 at 6 months v 1.34 ± 0.1 at 12 months, p=0.357) and although urea reduction ratio (URR) increased this did not achieve statistical significance (66.2 ± 1.3 v 69.2 ± 5.3 at 6 months v 69.5 ± 1.6 % at 12 months, p=0.062). In the control group there was no significant change over time for either eKt/v (1.3 ± 0.5 v 1.44 ± 0.1, p=0.438) or URR (67.9 ± 1.5 v 69.6 ± 2.1, p=0.148).

On examination of the individual factors influencing URR and the calculation of eKt/v, there was no significant change in the prescribed hours, prescribed blood flow, dialyser type or dialysate blood flow rate in either group. There was, however, a significant increase (p = 0.02) in the effective dialysis blood flow over time for the intervention group, which was not seen in the control group (p=0.433) (Figure 4.28). Post hoc analysis showed that although increases were observed at 6 months, the increase was not significantly different until 9 months and was maintained at 12 months.

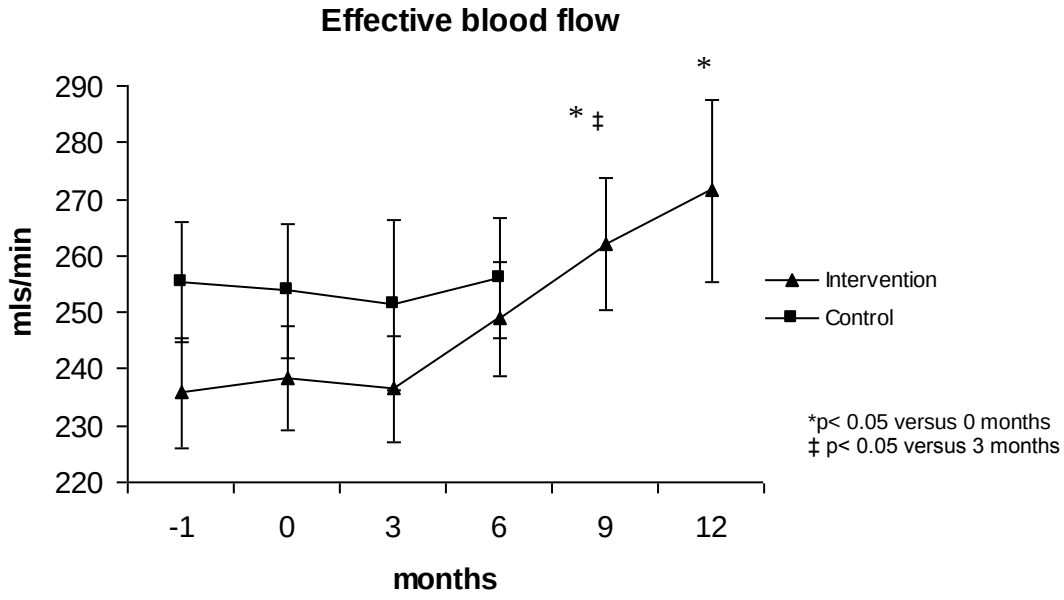


Figure 4.28: Effective dialysis blood flow (mean ± SEM) for the intervention group (-1, 0 & 3 months n= 25, 6 months n=20, 9 months n=16, 12 months n=13) and the control group (-1 month n=13, 0 month n=10, 3 months n=6, 6 months n=5) over time RM ANOVA shows the changes in mean dialysis blood flow are significant for the intervention group *F* (2.7, 30.7)= 4.1, p = 0.02.

4.9.2 Biochemistry

Table 4.11 provides a summary of the changes in biochemical results for groups over time. There were no significant differences noted for the majority of the variables in either group. There was, however, a significant (p = 0.038) reduction in post dialysis serum urea in the intervention group over time (Figure 4.29). Post hoc analysis demonstrated no significant difference between -1 month and 0 months and that a significant change did not occur until 9 months. While the control group and intervention group appear to follow the same pattern up to 6 months, the change in the control group was not significantly different (Figure 4.29).

Although not significant, trends (p = 0.087) were noted in the intervention group for an increase in pre dialysis serum bicarbonate and for a reduction in pre dialysis

serum potassium (p=0.078). Conversely, trends were also noted for a decreasing pre dialysis urea (p = 0.052) and decreasing pre dialysis creatinine (p = 0.051) in the control group which were not observed in the intervention group (Table 4.11).

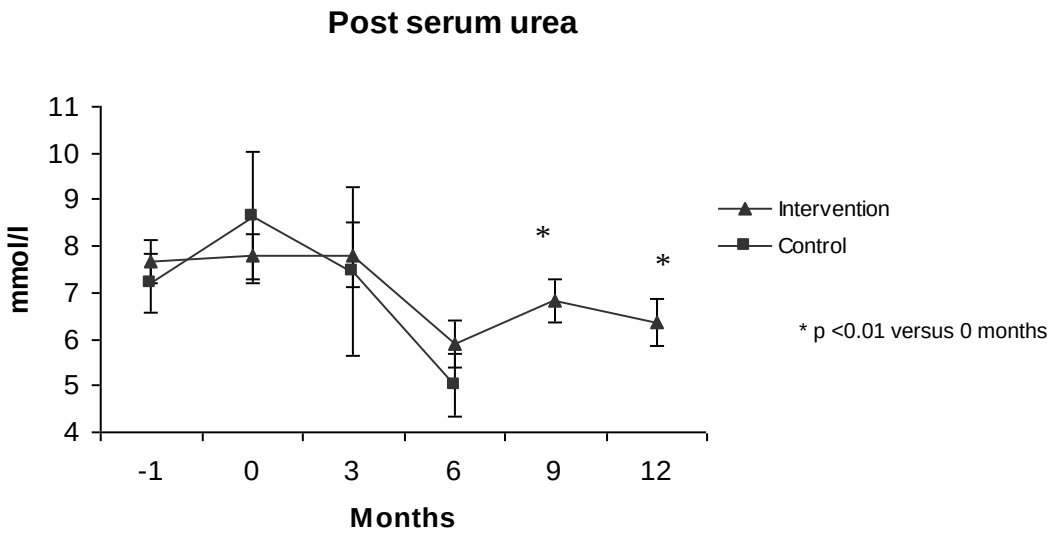


Figure 4.29: Post serum urea results (mean ± SEM) for the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5) over time. RM ANOVA shows the changes in post serum urea over time are significant for the intervention group *F* (2.6, 31.1) = 3.33, p = 0.038.

4.9.3 High sensitivity C-reactive protein

Although reductions in pre dialysis hsCRP (14.4 ± 20.5 v 11.7 ± 8.6 at 6 months v 8.3 ± 5.1 at 12 months) (p=0.171) and post dialysis hsCRP (15.0 ± 20.1 v 11.5 ± 8.9 at 6 months v 8.2 ± 5.5 at 12 months) (p=0.143) were observed in the intervention group, the changes were not statistically significant. There was also no significant change in pre dialysis hsCRP (20.6 ± 14.5 v 35.0 + 40.8 at 6 months) (p=0.353) or post dialysis hsCRP (19.3 ± 15.0 v 20.3 ± 3.7 at 6 months) in the control group (p=0.321). With the exception of the associations already highlighted no other associations with hsCRP were observed.

Table 4.11: Summary of changes in biochemistry

	Intervention				Control		
	-1 months n=25	**6 months** n=20	**12 months** n=13	**p**	**-1 months** n=13	**6 months** n=5	**p**
Pre dialysis sodium (mmol/l)	139.0 ± 2.7	138.3 ± 3.6	138.8 ± 2.5	0.812	137.5 ± 2.4	137.0 ± 4.2	0.872
Post dialysis sodium (mmol/l)	135.9 ± 2.2	136.5 ± 2.8	136.9 ± 2.2	0.469	135.7 ± 1.8	135.2 ± 1.3	0.541
Pre dialysis potassium (mmol/l)	5.2 ± 0.8	5.0 ± 0.9	4.7 ±` 0.7	0.078	5.1 ± 0.6	4.3 ± 0.3	0.138
Post dialysis potassium (mmol/l)	3.7 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	0.131	3.6 ± 0.5	3.4 ± 0.2	0.537
Pre dialysis bicarbonate (mmol/l)	21.7 ± 2.5	23.5 ± 2.5	22.1 ± 1.8	0.087	22.1 ± 2.6	22.8 ± 2.0	0.930
Post dialysis bicarbonate (mmol/l)	27.4 ± 2.6	27.5 ± 2.7	28.0 ± 3.2	0.285	28.0 ± 2.8	29.0 ± 3.1	0.339
Pre dialysis urea (mmol/l)	22.8 ± 6.0	19.6 ± 6.0	21.1 ± 6.2	0.129	22.3 ± 4.9	17.4 ± 3.2	0.052
Post dialysis urea (mmol/l)	7.7 ± 2.4	5.9 ± 2.2	6.4 ± 1.8	0.038	7.2 ± 2.3	5.0 ± 1.5	0.247
Pre dialysis creatinine (µmols/l)	876 ± 207.4	839 ± 175.6	860 ± 195.6	0.370	734 ± 218.7	635 ± 200.4	0.051
Post dialysis creatinine (µmols/l)	367 ± 91.1	332 ± 86.6	339 ± 71.0	0.111	293 ± 77.8	249 ± 61.5	0.429
Pre dialysis phosphate (mmol/l)	1.84 ± 0.4	1.65 ± 0.4	1.67 ± 0.4	0.165	1.64 ± 0.4	1.2 ± 0.4	0.139
Pre dialysis corrected calcium (mmol/l)	2.40 ± 0.2	2.40 ± 0.1	2.32 ± 0.1	0.272	2.42 ± 0.2	2.4 ± 0.1	0.835
Pre dialysis albumin (g/l)	36.5 ± 2.9	38.1 ± 2.5	37.8 ± 3.0	0.452	37.8 ± 3.0	37.0 ± 2.5	0.107

Results are presented as mean ± SEM

4.9.4 Leptin

The results for leptin were hampered by a significant number of missing samples in both groups at all of the time points. The results presented are based on the available samples at each time point and are not necessarily for the same individuals.

Pre dialysis results for the intervention group are based on n= 11 for -1 month, n = 10 for baseline, n = 8 for 3 months, n = 13 for 6 months, n= 8 for 9 months and n = 4 for 12 months. Pre dialysis results for the control group are based on n= 9 for – 1 month, n = 8 for baseline, n = 3 for 3 months and n = 2 for 6 months (Figure 4.30).

The post dialysis results for the intervention group are based on n = 12 for – 1 month and baseline, n = 8 for 3 months, n = 9 for 6 months, n= 4 for 9 months and n = 3 for 12 months. The post dialysis results for the control group are based on n = 9 for – 1 month, n = 5 for baseline, n = 3 for 3 months and n= 2 for 6 months (Figure 4.31).

At the point of recruitment the available results demonstrate the presence of hyperleptinaemia in both groups (normal range 3.84-7.36 µg/l). Unfortunately little else can be reliably inferred.

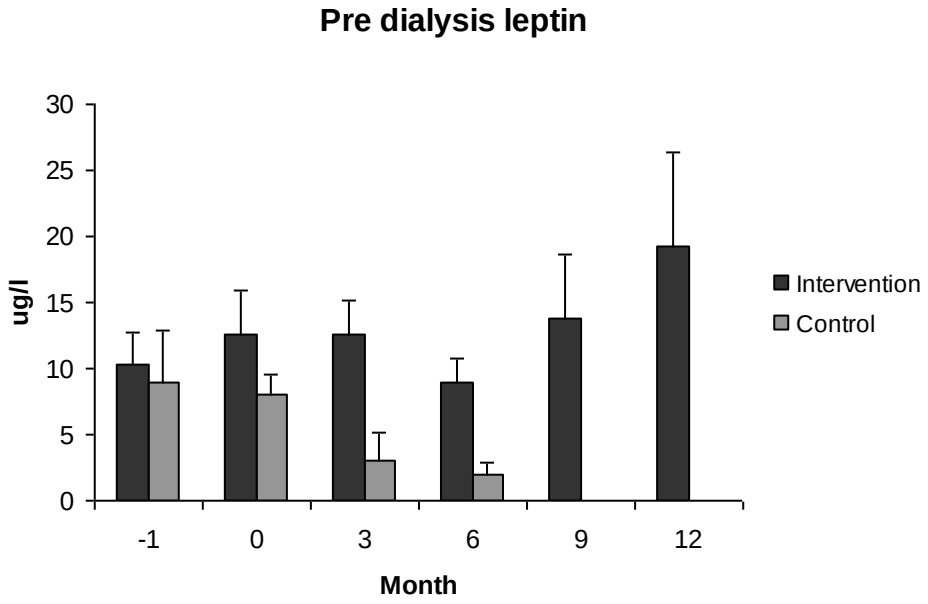


Figure 4.30: Pre dialysis serum leptin over time for the intervention and control group (mean ± SEM).

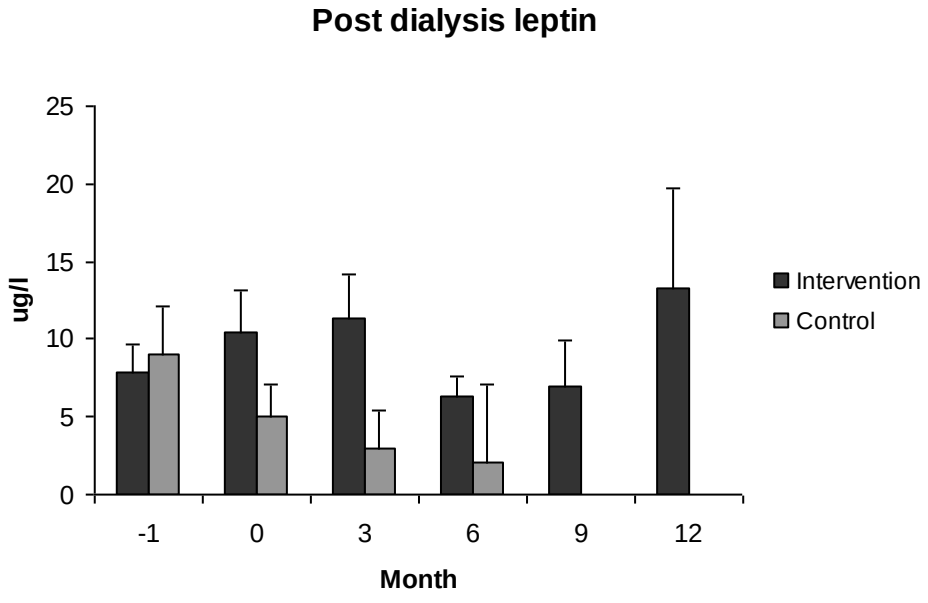


Figure 4.31: Post dialysis serum leptin over time for the intervention and control group (mean ± SEM)

4.9.5 Haemoglobin and ESAs

A significant (p= 0.041) increase in haemoglobin was observed over time in the intervention group and conversely a significant (p= 0.04) decrease in haemoglobin was observed over time in the control group (Figure 4.30). Post hoc analysis shows the change was significant at 6 months for both groups.

In the intervention group there was a trend towards an increase in haematocrit (Hct) over time (34.3% ± 5.0 v 36.6% ± 4.0 at 6 months v 38.0% ± 3.8 at 12 months) (p=0.058). Conversely there was a decrease in Hct over time in the control group (35.6% ± 4.6 v 33.2% ± 4.0), but this was not statistically significant (p=0.155).

The ESA/Hct index significantly (p = 0.018) decreased in the intervention group over time, with no significant (p=0.224) change observed over time in the control group (Figure 4.32). Post hoc analysis demonstrated a significant reduction at 3 months with a further significant reduction at 6 months.

The weekly prescribed ESA dose decreased significantly (p = 0.029) over time in the intervention group. Post hoc analysis shows a significant reduction in ESA dose occurred a 6 months. Conversely, the weekly prescribed ESA dose did not change significantly (p = 0.227) over time in the control group (Figure 4.31). No patients in either group received IV Iron beyond the standard maintenance dose. In turn the weekly patient costs associated with the prescription of ESA significantly (p = 0.029) decreased over time in the intervention group from £72.54 ± 9.74 to £51.87 ± 9.0 (BNF 2009). In the control group although the weekly patient cost associated with the prescription of ESA increased over time from £77.50 ± 16.6 to £96.10 ± 35.50, it did not achieve statistical significance (p = 0.227) (Figure 4.33).

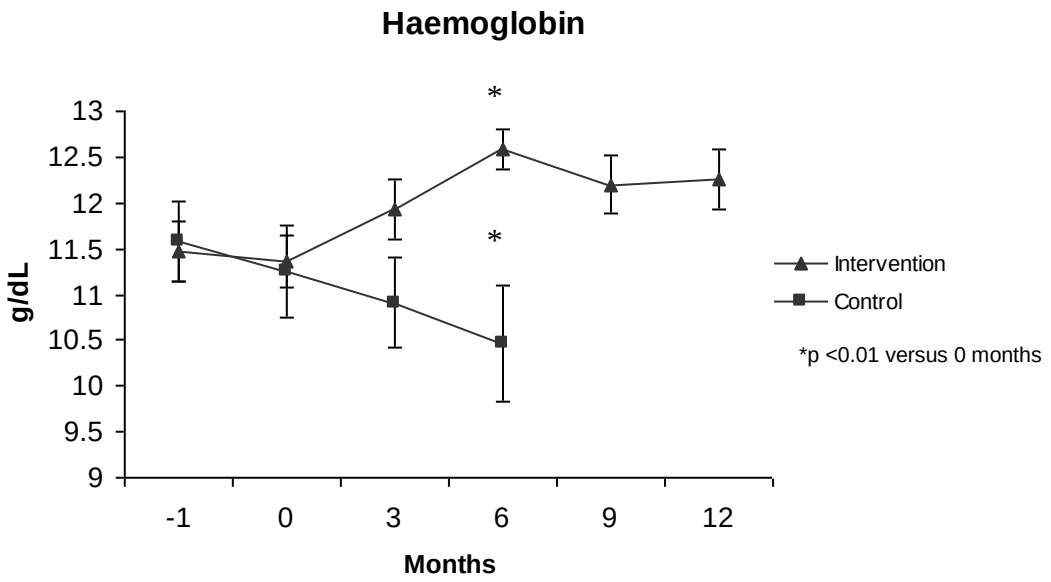


Figure 4.32: Haemoglobin levels (mean ± SEM) over time for the intervention group (at -1, 0 and 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and the control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5. RM ANOVA shows the change is significant for both the intervention group *F* (2.1, 25.3) = 3.57, p = 0.041 and the control group *F* (2.1, 8.5) =4.75, p = 0.04.

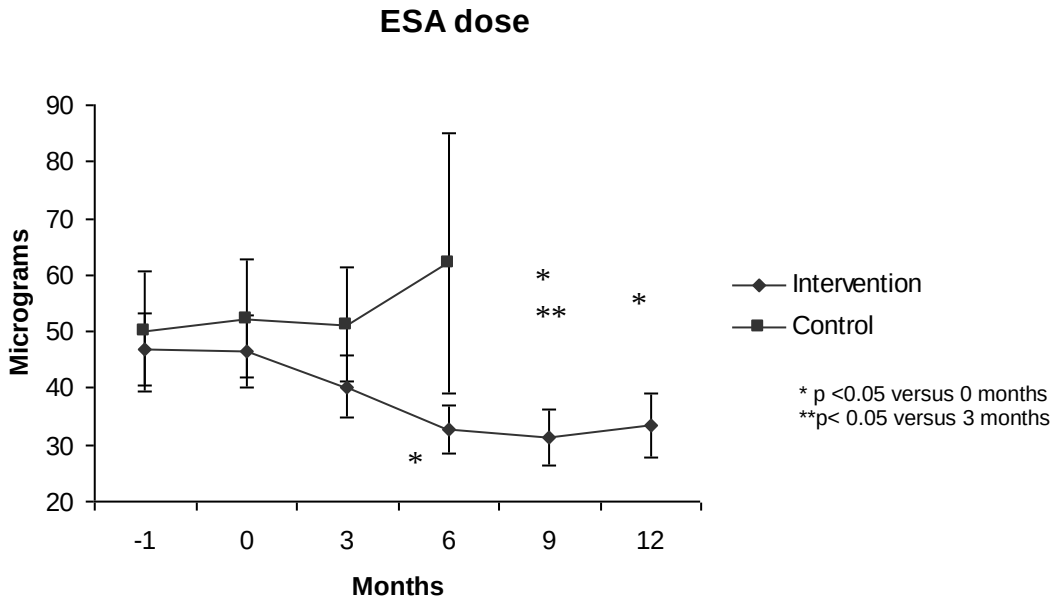


Figure 4.33: Changes in erythrocyte stimulating agent (ESA) dose (mean ± SEM over time) in the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16 and at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5) RM ANOVA shows the changes over time are significant for the intervention group *F* (1.2, 14.9) = 5.38, p = 0.029.

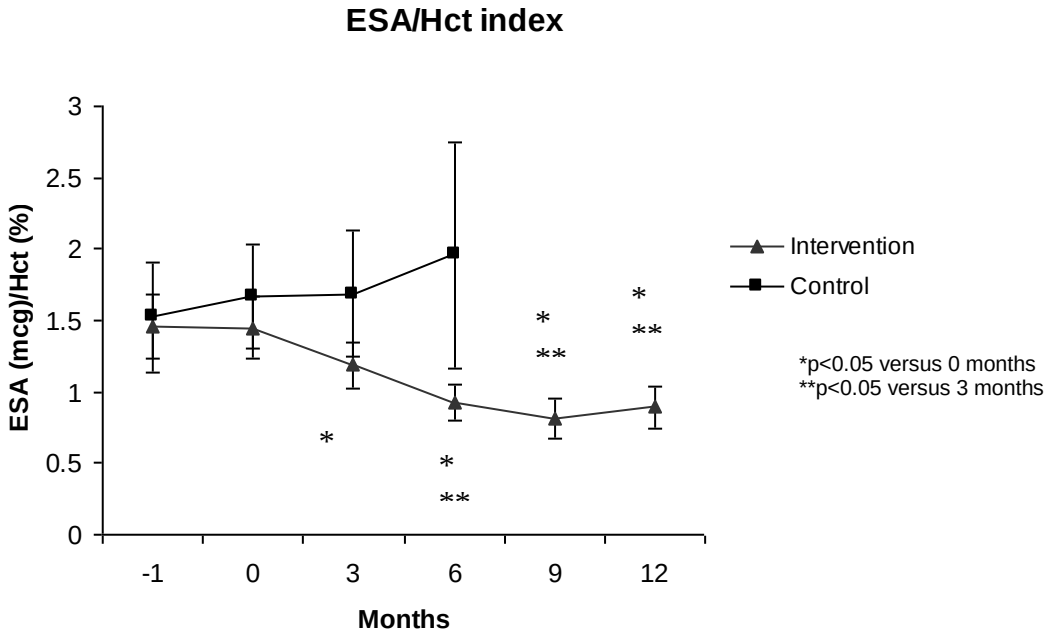


Figure 4.34: Erythrocyte stimulating agents /haematocrit index (ESA/Hct) (mean ± SEM) over time in the intervention group (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5). RM ANOVA shows the changes over time are significant for the intervention group F (1.2, 13.9) = 7.1, p = 0.018.

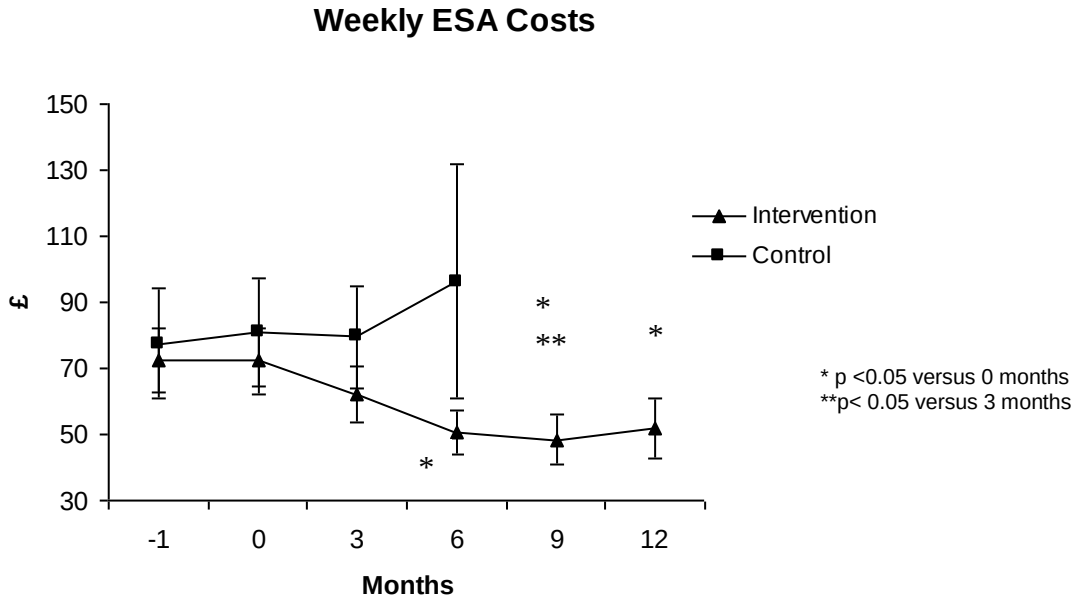


Figure 4.35: Weekly costs of erythrocyte stimulating agents (ESA) (mean ± SEM) over time for the intervention (at -1, 0 & 3 months n= 25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6 and at 6 months n=5). RM ANOVA shows the changes over time are significant for the intervention group F (1.24, 14.9) =5.38, p = 0.029.

4.9.6 Blood pressure, antihypertensives and phosphate binders

There was a significant (p=0.048) decrease in systolic blood pressure (SBP) observed over time in the intervention group. Post hoc analysis shows this change was significant at 6 months and 9 months. No significant (p=0.686) change was observed over time in the control group (Figure 4.36). There was no significant change in diastolic blood pressure seen over time in the intervention (78.8 ± 2.5 v 77.8 ± 2.5 mmHg, p=0.195) or the control group (77.2 ± 4.0 v 78.4 ± 7.0 mmHg, p=0.536). There was also no significant change in interdialytic weight gains in the intervention group (1.3 ± 0.1kg v 1.2 ± 0.2kg, p=0.486) or in the control group (1.12 ± 0.2 v 1.44 ± 0.3, p=0.721).

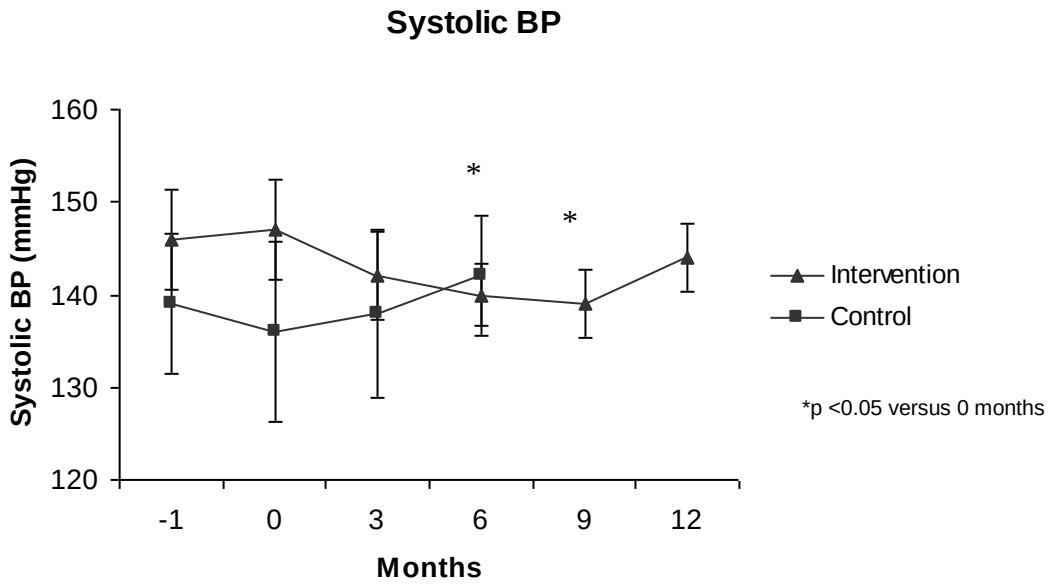


Figure 4.36: Pre dialysis systolic blood pressure for the intervention group (at -1, 0 & 3 months n=25, at 6 months n=20, at 9 months n=16, at 12 months n=13) and control group (at -1 month n=13, at 0 month n=10, at 3 months n=6, at 6 months n=5 (mean ± SEM). RM ANOVA shows the changes over time are significant for the intervention group *F* (3.1, 37.1) = 2.87, p = 0.048.

The mean total daily dose of antihypertensives (mg/day) decreased over time in the intervention group by 27 mg/day, but did not achieve statistical significance (p=

0.086). The mean total daily dose in the control group did not change significantly over time (p=0.374). The individual daily prescribed doses of antihypertensives were examined for the intervention group. Results showed that the daily dose of beta-adrenoreceptor blockers decreased by 60% over time, but was not significant (p= 0.193). The daily dose of calcium channel blockers increased by 21% but was not statistically significant (p=0.273). There was also a non-significant increase of 6% in the daily dose of angiotensin –II receptor antagonists (p>0.05). The daily dose of angiotensin- converting enzyme inhibitors decreased by 21%, but was not significant (p= 0.330). The daily dose of alpha-adrenoreceptor blocking drugs increased by 33%, but was not statistically significant (p= 0.337) (Figure 4.37).

There was no significant change in the number of phosphate binders prescribed in either the intervention group (4.2 $\pm$ 0.4 v 4.2 $\pm$ 0.7, p=0.477) or the control group (2.24 $\pm$ 0.6 v 1.8 $\pm$ 0.8, p>0.05).

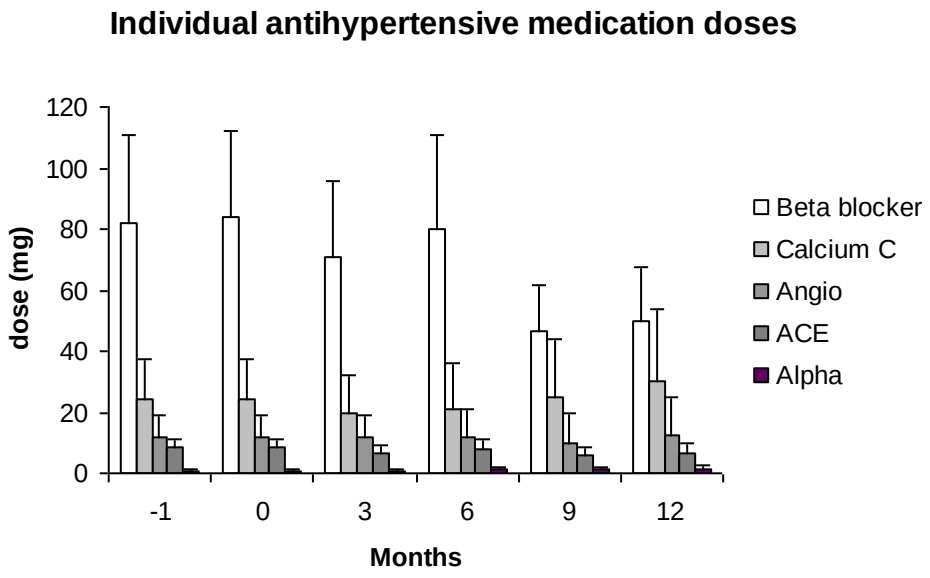


Figure 4.37: Prescribed doses of specific antihypertensive drugs in the intervention group (n= 25 at 3 months, n=20 at 6 months, n =16 at 9 months n=13 at 12 months) (mean $\pm$ SEM) RM ANOVA demonstrated no significant changes over time.
Beta blocker= beta-adrenoreceptor blockers; Calcium C= Calcium channel blocker; Angio= angiotensin –II receptor antagonists; ACE= Angiotensin-converting enzyme inhibitors; Alpha = Alpha-adrenoreceptor blockers

CHAPTER 5: DISCUSSION

The results of this 12 month progressive low to moderate intensity intradialytic exercise intervention suggest that improvements in function, quality of life, nutritional status and clinical status are possible secondary to such an intervention. The results also suggest that improvements in functional performance are associated with several of the observed improvements in nutritional status and clinical status.

5.1 PATIENT CHARACTERISTICS

The results of the exercise intervention indicate that the recruited population were more representative of the prevalent Scottish HD population, as the age of the recruited population better reflected the age of the prevalent Scottish dialysis population (58.4 years v 65.3 years) (SRR 2007). In addition, the gender profile in the present study mirrored the profile observed in the prevalent Scottish dialysis population (SRR 2007). Furthermore, in comparison to many of the previous intradialytic aerobic studies the patients in the present study were approximately 10 years older (Frey et al 1999, Painter et al 2002, Moug et al 2003, Macdonald et al 2005, Storer et al 2005) and had a longer dialysis vintage (Miller et al 2002, Painter et al 2002, Parsons, Toffelmire & King-VanVlack 2004, Macdonald et al 2005, Parsons, Toffelmire & King-VanVlack 2006), with only one previous study reporting a longer dialysis vintage (Storer et al 2005).

The profile of primary diagnosis in the intervention group was not, however, wholly representative, of the prevalent Scottish HD population as no patients with diabetes volunteered for the intervention. Despite this, the recruited population had similar

levels of comorbidity to that of the prevalent Scottish population (Khan et al 1993, Metcalfe et al 2000). They also had higher levels of comorbidity than has been reported in previous intradialytic exercise studies (Miller et al 2002, Parsons, Toffelmire & King-VanVlack 2004, Storer et al 2005, Parsons, Toffelmire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008). Although there were two significant differences between the groups at recruitment (bodily pain and sit to stand performance, discussed in Section 5.3), there was no significant difference in any of the outcome measures in either group between recruitment (-1 month) and baseline (0 months). This clearly indicates that a stable population was recruited and that a significant month to month variation in the outcome measures was not the norm.

Past exercise studies have been criticised for recruiting the healthiest haemodialysis patients who are not representative of the wider HD population (Johansen 2005). It is, therefore, considered that the present study has gone some way to addressing this particular limitation. These findings also suggest, as per the intention of the study design that the exercise protocol in the present study was broadly applicable, and was suitable for older patients with a longer dialysis vintage and a higher level of comorbidity.

In the present study, the rate of withdrawal from the exercise intervention group was 0% at 3 months, 20% at 6 months, 36% at 9 months and 48% at 12 months. These rates although appearing high are better or similar to previous studies of intradialytic aerobic exercise. For studies of 3 months duration or less the average withdrawal rate was 21% (Moore et al 1993, Moug et al 2003, Parsons, Toffelmire & King-VanVlack 2004) versus 41% for those studies of 5-6 months duration (Miller et al 2002, Painter et al 2002, Anderson, Boivin & Hatchett 2004, Parsons, Toffelmire &

King-VanVlack 2006). Withdrawal rates from the control group were similar to rates of withdrawal from other intradialytic exercise studies with control groups. Parsons, Toffelimire and King-VanVlack (2004) reported a 22% withdrawal at 2 months and Moug et al (2003) reported a 14% withdrawal at 1 month.

The results suggest that for both groups, concurrent medical events, unrelated to the exercise intervention, rather than a lack of motivation were the most frequent reasons for withdrawal, a finding which concurs with previous studies of intradialytic exercise (Moore et al 1993, Painter et al 2002, Moug et al 2003, Macdonald et al 2005, Parsons, Toffelmire and King-VanVlack 2006). In addition, the comorbidity risk profile, age and dialysis vintage of the patients remaining in the study at 12 months was similar to that at recruitment suggesting that these factors did not influence withdrawal.

5.2 EXERCISE PROTOCOL

The results demonstrate that patients progressively increased the duration of their thrice weekly exercise sessions as was instructed in the exercise protocol. This is shown by a significant difference in the duration of the exercise sessions between 3 months and all other months and by a non-significant difference in the duration of exercise sessions between subsequent months. Furthermore, the results also show that as instructed patients significantly increased their level of resistance between 3 months, 6 months and 9 months. This indicates that the protocol was broadly applicable as intended and could be easily followed by patients and implemented by dialysis staff. Unexpectedly, there was no subsequent significant increase in the level of resistance between 9 and 12 months. On further investigation, it would appear from the available exercise logs that from 9 months onwards patients, during

the two weekly sessions that were not individually supervised, largely maintained the 9 month levels of resistance. It is, therefore, unlikely that patients were consistently achieving an RPE of 12-13 which suggests further increases in overload were minimal beyond 9 months. In effect between 9 and 12 months patients appeared to enter a maintenance phase. Whilst it would be important to explore whether this was as a result of diminishing motivation, it could also suggest that patients and/or dialysis staff require further education about the need to continually progress overload.

The number of weekly exercise sessions undertaken by patients in the present study resulted in an overall participation rate of 82%. Whilst few previous intradialytic studies report participation rates; those that do, report slightly higher rates of approximately 87% (Moore et al 1993, Frey, Mir & Lucas 1999, Storer et al 2005, Toussaint, Polkinghorne & Kerr 2008). However, these were all short term studies of 2-3 months duration and with the exception of one study (Toussaint, Polkinghorne & Kerr 2008); they involved individual supervision of each exercise session (Moore et al 1993, Frey, Mir & Lucas 1999, Storer et al 2005). The participation rates in the present study are also favourable when compared to longer studies of 6 months duration. In one study (Painter et al 1986) where a switch at 3 months from individual supervision of each exercise session to general supervision occurred, there was a drop in participation from 91% to approximately 75%. In addition, in another intradialytic exercise study of 6 months duration, where only general supervision by dialysis staff was used, participation rates were reported as 56% (Miller et al 2002). It would, therefore appear that the approach to supervision in the present study produces comparable participation rates to those utilising individual supervision of each exercise session. It would also appear that in the longer term, maintaining one individually supervised exercise session produces

better participation rates than those only utilising general supervision by dialysis staff.

In previous intradialytic aerobic studies common reasons reported for non-participation in exercise sessions have been clinical events including viral infections, needle problems, fluid overload, acute illness and hospital admission (Moore et al 1993, Painter et al 1986, Frey, Mir & Lucas 1999, Storer et al 2005). In the present study, although such reasons did contribute to non-participation, they were not the most common. Instead, in the present study, the most common documented reasons were 'dialysis staff were too busy' or 'otherwise occupied' and the 'patient didn't want to'. This finding could suggest the existence of barriers on the part of dialysis staff to facilitate or encourage patients to exercise and has been reported elsewhere. In a study by Painter et al (2004) dialysis staff reported a number of barriers to encouraging patients to exercise. The most common reported barriers were the perception that patients lack motivation; that dialysis staff perceive a lack of responsibility for encouraging exercise; that dialysis staff lack the ability to motivate patients to exercise and the increasing employment of unqualified staff versus qualified staff (Painter et al 2004). Other evidence from a patient perspective suggests that a lack of encouragement from dialysis staff to exercise, and dialysis staff frequently expressing concerns over the risk of equipment related injuries to themselves, can act as barriers for patients (Kontos et al 2007). In the present study, patients also reported a lack of encouragement and motivation on the part of some dialysis staff. In addition, some dialysis staff reported that the cycle ergometer was cumbersome and that they were concerned about possible lifting and handling risks. This would suggest that, should it be the case that dialysis staff are relied upon to deliver exercise programmes, further or ongoing education and training would be required to optimise patient participation. It would also suggest that the

type of equipment can act as a direct barrier and that there is perhaps a need for alternative lighter, less cumbersome equipment suitable for the dialysis setting.

5.3 EFFECT OF EXERCISE ON FUNCTION

Despite the staff and equipment difficulties, the exercise programme produced several clear benefits and significant positive associations were found between levels of resistance and objective measures of function (timed up and go, sit to stand, handgrip). This would suggest that as a progressive increase in overload occurred it elicited progressive improvements in function. The positive association between the levels of resistance and timed up and go was seen at every time point and strengthened over time, but the association for sit to stand and handgrip strength was lost at 12 months. In addition to the associations between levels of resistance and function, an association was also found with calf muscle circumference (CMC) at 3, 6 and 9 months. As CMC is considered to reflect lower limb FFM this suggests that as the level of resistance progressively increased so did lower limb FFM. This association was also lost at 12 months, possibly due to diminishing patient numbers.

At recruitment, the values for sit to stand performance between the two groups were significantly different, suggesting that the control group had lower levels of muscle endurance and higher fatigability than the intervention group. The reason for this difference is unclear. However, as the only other significant difference between the two groups at recruitment was for perceived levels of bodily pain, it is possible that the difference is related to this. The difference in perceived bodily pain between the groups implies that the control group had higher levels of bodily pain which they considered interfered with their daily activities.

Although there is a lack of comparable normative data, at recruitment the values for sit to stand performance were 60% lower than those reported for healthy individuals who were 10 years older than the recruited population (Ritchie et al 2005). In comparison with other observational or exercise intervention studies of HD patients, the results at recruitment were similar (McIntyre et al 2006) or 20-35% lower (Cappy, Jablonka & Schroeder 1999, Koufaki, Mercer & Naish 2002a, Majchrzak et al 2005, Majchrzak et al 2007). Therefore, the results at recruitment in the present study confirm that HD patients exhibit lower levels of physical function than healthy individuals. In addition, the results at recruitment suggest that in comparison to previous studies, the present study recruited a lower functioning group. This reinforces the view that physical functioning is negatively impacted by a longer dialysis vintage, higher comorbidity risk and older age (Johansen et al 2003b, Chumlea et al 2003, Stack et al 2005, Lopes et al 2007) and are important issues to consider in providing a representative sample of the prevalent population.

Over the course of the present study, sit to stand performance in the intervention group significantly improved by 49%. The first significant increase in sit to stand performance was observed at 3 months (+25%) which was in comparison to a non significant decline in the control group. Between 3 and 6 months another increase in the number of sit to stand transitions was observed in the intervention group (+4%), but this was not statistically significant. Conversely, a further non-significant decline was noted in the control group between 3 and 6 months giving rise to an overall 26% decline at 6 months. These observed changes in the control group would support the view that the changes in the intervention group at 3 and 6 months are as a result of the exercise intervention. Between 6 months and 9 months the intervention group demonstrated another significant increase (+13%) in the number of sit to stand transitions and a further small non-significant increase (+6%) between

9 and 12 months. The reason for a non significant improvement between 3 to 6 months despite a significant increase in resistance over the same period is unclear. However, it may reflect non-linear improvements in endurance and/or strength. There was also no further significant improvement between 9 and 12 months, but this could be explained by the apparent non-significant increase in overload preventing further significant gains in lower extremity strength and/or endurance.

The results demonstrate that the exercise intervention improved endurance, muscle power and muscle fatigability (Koufaki & Mercer 2006). The improvement seen at 3 months was of the greatest magnitude in comparison to subsequent months and occurred during the low intensity phase (level 1 & 2) of the programme. It would therefore appear that an initial low intensity programme in older, lower functioning patients over a 3 month period is sufficient to derive positive benefits and that further benefits can then be gained using a longer term moderate intensity programme.

While none of the previous intradialytic exercise studies examined changes in sit to stand 60 second performance, improvements in sit to stand 60 second performance have been seen in other types of HD exercise studies. Cappy, Jablonka & Schroeder (1999) reported an improvement of 21% at 3 months, a further 11% at 6 months and a further 26% at 12 months, as a result of a combined aerobic and resistance intervention immediately before dialysis. Cook, MacLaughlin & Macdougall (2008) in their 12 month combined weight loss and interdialytic exercise study of overweight stage 4 CKD, HD & PD patients observed an overall 30% increase in sit to stand performance. Koufaki, Mercer & Naish (2002a) in their 3 month inter/intradialytic aerobic study of PD & HD patients reported a 27% increase. It therefore appears that the exercise protocol in the present study was able to

produce the same magnitude of change seen in other higher intensity interventions involving younger, higher functioning patients.

Sit to stand performance demonstrated significant strong positive correlations with timed up and go at 3, 6, 9 and 12 months. This relationship implies that improvements in sit to stand performance are positively associated with improvements in timed up and go performance. Given that the action of standing from a seated position is one component of the timed up and go test this association is perhaps not unexpected. In addition to this association, sit to stand performance demonstrated a consistently strong significant correlation with handgrip strength at 3, 6 and 9 months. Such an association between measures of upper and lower limb strength have been reported elsewhere and have been suggested to reflect overall increases in muscle strength (Rantanen 2003). There was also an association between sit to stand and CMC at 3 and 6 months, which weakened slightly from 3 to 6 months. Such an association could imply that increases in FFM are influencing function, which would not be unexpected. Whilst the loss of the association after 6 months could again be due to diminishing patient numbers, it may also suggest that latterly the changes in sit to stand performance were due to changes in the functionality of existing FFM.

Due to the non-invasive nature of the present study, it was not possible to examine the underlying mechanisms that resulted in the observed improvements in sit to stand performance. However, it can be hypothesised that a progressive increase in physical activity has progressively reversed some or all of the known abnormalities in muscle metabolism and morphological structure (Koudi et al 2001, Sakkas et al 2003). It could also be hypothesised that, based on the association between CMC and sit to stand, increases in lower limb FFM contributed to some of the change

seen. Whilst it is not unreasonable to assume that some of the improvements in function could be attributable to the observed significant increase in haemoglobin, there was no association between the changes in haemoglobin and sit to stand (or TUG, handgrip strength). A previous intradialytic exercise study demonstrated that in patients with pre-existing haematocrit levels greater than 30% further increases in haematocrit and haemoglobin did not further influence exercise capacity (Painter et al 2002). This may therefore explain the lack of observed association in the present study.

In contrast to the sit to stand performance, the time taken to complete the timed up and go (TUG) test, did not differ significantly between the two groups at recruitment. This suggests that both groups had similar levels of dynamic balance and mobility. Again, although there is a lack of comparable normative data, a meta analysis by Bohannon (2006) states a mean normative time of 8.1 seconds for individuals aged 60-69 years and a time greater than 9 seconds to be worse than average. The time taken to complete the timed up and go at recruitment in the present study was slower than 9 seconds, thereby suggesting that both groups at recruitment had significant impairments of dynamic balance and mobility.

To date, few studies within the HD population have utilised the TUG test thereby limiting comparisons. One intradialytic exercise study using TUG as an outcome measure reported a faster mean time of 7.56 seconds at baseline (Storer et al 2005). However the recruited population was 10 years younger than in the present study and appeared to have lower levels of comorbidity. A non-exercise study in HD patients (Jamal et al 2006) also utilised the TUG test and reported a slower TUG of 13.6 seconds than seen in the present study. However, in this instance the population was 10 years older than in the present study. While one interdialytic

exercise study also used the TUG test, they did not publish initial baseline values, thereby preventing comparisons (Cook, MacLaughlin & Macdougall 2008). Therefore, from the limited evidence in the HD population, it would appear that the results at recruitment in the present study are not uncharacteristic of an older HD population.

Over the course of the present study, patients in the intervention group demonstrated significant improvements in the time taken to complete the TUG. The patients in the intervention group were significantly faster (+15%) at 3 months and again significantly faster at 6 months (+ 2%). Although the results for the control group suggest some variability between baseline and 3 months, at 6 months they are no faster or slower than at recruitment. These results would support the view that the changes observed in the intervention group at 3 and 6 months are as a result of the intervention. Beyond 6 months the intervention group demonstrated further significant improvements in time at 9 months (+7.5%) and again at 12 months (+6%). At 12 months the patients in the intervention group were completing the test in a time that was 25% faster than at recruitment. Similar to the sit to stand results the greatest magnitude of change was seen at 3 months, suggesting again that an initial low intensity programme in older, lower functioning patients is sufficient to derive positive benefits. The continued significant improvements in TUG between 9 months and 12 months in the absence of any significant changes in resistance or sit to stand performance, could suggest factors other than improvements in lower extremity strength and endurance are influencing the ability to complete the TUG test in a faster time. As the TUG test is a test with a number of components, it is possible that the exercise intervention beyond 9 months has resulted in ongoing improvements in gait and postural balance, which would also influence the ability to complete the TUG in a faster time (Messier et al 2000, Wall et al 2000, Netz et al

2004). However, it perhaps cannot be ruled out that latterly patients were able to complete the test in a faster time due to increasing familiarisation and confidence.

Improvements in TUG have also been seen in the few CKD exercise studies using TUG as an outcome measure. One intradialytic study (Storer et al 2005) of a younger population, with a longer dialysis vintage saw an improvement of 14% after 3 months due to 40 minutes of thrice weekly higher intensity aerobic interval training. This is a similar improvement to that seen at 3 months in the present study. Cook, MacLaughlin & Macdougall (2008) reported in a younger obese CKD population (HD, PD and Stage 4 CKD) an overall improvement of 37% in TUG over a 12 month period. Although the change in the latter study was of a greater magnitude than seen in the present study, the accompanying weight loss in this instance could have augmented the improvement seen (Sternfeld et al 2002).

Overall the improvements in TUG observed in the present study suggest that in an older lower functioning population the use of a progressive low to moderate intensity intervention can result in significant progressive improvements in mobility and dynamic balance. Additionally, as TUG performance has been negatively associated with disability and falling risk the observed improvements are likely to have wider implications (Bohannon 2006).

There was no significant difference in handgrip strength between the intervention group and the control group at recruitment. Although differences in equipment and methodology will result in some variance of results, the results for handgrip strength at recruitment were approximately 70% of expected values for healthy individuals of the same age (Kuh et al 2005). The results for handgrip strength at recruitment are lower than those observed in a 3 month interdialytic resistance intervention (Headley

et al 2002), but the population in the study were 15 years younger than that in the present study. However, the handgrip strength results at recruitment are consistent with those found in non exercise studies of similarly aged HD patients (Qureshi et al 1998, Limaye et al 2001). Consequently, the handgrip strength findings in the present study suggest that both the control and intervention group at recruitment had poor upper limb strength and that this was despite the appearance of adequate upper FFM stores (as indicated by MAMC results). The findings also suggest that the recruited group would as a consequence have a higher disability, cardiovascular and all cause mortality risk (Al-Snih et al 2002, Qureshi et al 2002, Rantanen et al 2003).

Further to the significant improvements in sit to stand and TUG performance, significant progressive increases in handgrip strength were also observed in the intervention group over the course of the study. The first significant increase in handgrip strength (+9%) was observed at 3 months. There was also a further improvement in handgrip strength between 3 and 6 months (+6%), but this was not statistically significant. As the pattern of change for handgrip strength was the same pattern for sit to stand performance, this may again suggest non-linear improvements in handgrip strength. In comparison the results for the control group, although suggesting some variability in the results at 3 or 6 months, demonstrated no significant change in handgrip strength. This is therefore considered to support the view that the changes observed in the intervention group are as a consequence of the exercise intervention. Between 6 months and 9 months the improvements in handgrip strength were maintained by the intervention group and then a further significant improvement occurred between 9 and 12 months (+10%). Again the lack of a significant change between 6 and 9 months could suggest non-linear changes in handgrip strength. As the significant change between 9 and 12 months occurred

in the absence of further significant improvements in resistance or sit to stand performance, this may suggest that, like TUG, other mechanisms are positively influencing changes in handgrip strength.

As handgrip strength has previously been negatively associated with vascular compliance in CKD patients (Gu et al 2008), one possible mechanism that could be influencing the ongoing changes in handgrip strength is changes in vascular compliance. It is known that improvements in vascular compliance can occur secondary to improvements in endothelial function in response to regular aerobic exercise in both normotensive and hypertensive individuals (Higashi et al 1999). Such an effect of aerobic exercise on vascular function in HD patients has also been demonstrated in one intradialytic exercise study of 3 months duration (Toussaint, Polkinghorne & Kerr 2008) and in one interdialytic study of 3 months duration (Mustata et al 2004). Additionally, improvements in vascular function could also be related to the observed decrease in ESA dose, as ESA is known to cause an increase in endothelin-1 which negatively influences vascular function (Kanbay et al 2007).

There is also a known negative association between handgrip strength and insulin resistance in healthy individuals (Lazarus, Sparrow and Weiss 1997). As skeletal muscle is known to be one of the major sites of insulin mediated glucose disposal it is possible that changes in the physiology of these muscles can result in changes in peripheral sensitivity to insulin and handgrip strength (Lazarus, Sparrow and Weiss 1997). Although one small 3 month study of interdialytic aerobic exercise in non diabetic HD patients, did not demonstrate improvements in insulin sensitivity (Mustata et al 2004), a 12 month interdialytic aerobic study of latterly high intensity training in young healthy non diabetic HD patients did demonstrate improvements in

insulin sensitivity (Goldberg et al 1986). Therefore, it is conceivable that a 12 month low to moderate intensity programme in older low functioning patients could elicit improvements in insulin sensitivity.

In addition to the association between handgrip strength and sit to stand, an association was also found between CMC and handgrip, but not MAMC and handgrip strength. The association implies that as lower limb FFM increased, handgrip strength improved. It is possible that CMC is acting as a marker for cardiovascular related improvements which have positively impacted on handgrip strength. This argument is strengthened by a large observational study of older adults observing a negative association between calf measurements and carotid plaques, such that carotid plaque formation was less frequent with increasing calf measurements (Debette et al 2008).

Although inflammation has been negatively associated with handgrip strength in studies of the general population (Barbieri et al 2003, Hamer and Molloy 2009) and HD patients (Qureshi et al 1998), there was no association between handgrip strength and hsCRP in the present study. Nor was there any relationship between hsCRP with sit to stand performance or TUG. This suggests, and as other studies have shown, that improvements in function can still occur in the presence of low grade inflammation (Hung et al 2002, Johansen et al 2003b, Spruit et al 2005). It would also suggest that physical inactivity and atrophy of muscles have a greater influence on function than low grade inflammation. However it is possible that a decrease in the local expression of proinflammatory cytokines in muscle has occurred which has not been accurately reflected in serum hsCRP values (Spate and Schulze 2004).

Previous studies of intradialytic exercise have not utilised handgrip as an outcome thereby preventing direct comparisons. There is, however, one 3 month resistance exercise study in HD patients, which reported no significant change in handgrip (Headley et al 2002). This study was a smaller study, involving patients who were 15 years younger than those in the present study and who had significantly higher handgrip strength values at baseline. It is, therefore, possible that the intervention in this instance was not of sufficient intensity to elicit improvements. It is, however, worth noting that changes in handgrip strength of a similar magnitude have been seen in a large cardiac rehabilitation study which also utilised an aerobic intervention (Mroszczyk-McDonald, Savage & Ades 2007).

Similar to the results for handgrip strength and timed up and go, there was no significant difference in the physical component summary (PCS) score between the control and intervention group at recruitment. This suggests that at recruitment both groups had similar perceptions of their own functional ability and well being. In comparison to the general population norm score of 50 (Ware et al 2007), the reported PCS scores at recruitment were significantly lower. This implies that patients in both groups perceive themselves to have physical limitations, a finding which is consistent with previous studies (De Oro 1997, Diaz-Buxo et al 2000, Kutner et al 2000b, Lamping et al 2000, Tawney et al 2000, Mittal et al 2001, Allen et al 2002, Dwyer et al 2002, Lowrie et al; 2003, Knight et al 2003, Perlman et al 2005). Specifically the results of the physical domain scores suggest that patients perceive they are limited in physical activities such as walking distances and climbing stairs (PF), that they have difficulty in completing tasks such that they accomplish less than they would like to (RP) and that they perceive their general health as poor (GH) and likely to get worse. As stated previously these scores also

suggest that the control group, but not the intervention group perceive bodily pain (BP) as a limiting factor in their daily activities.

The PCS scores at recruitment in the present study are similar to large observational studies of similarly aged HD patients, (De Oreo 1997, Kalantar-Zadeh et al 2001, O'Sullivan and McCarthy 2007, Dwyer et al 2002, Cleary and Drennan 2004). This also remains the case when the PF, RP, BP and GH domain scale scores are compared (Khan et al 1995, Merkus et al 1997, O'Sullivan and McCarthy 2007, Kutner, Zhang and McClellan 2000, Cleary and Drennan 2004). However, in comparison to the three studies of intradialytic aerobic exercise who reported SF36 scores, the results at recruitment in the present study again imply that a lower functioning group has been recruited (Painter et al 2002, Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-VanVlack 2006). Once more these differences could be explained by the older age, the longer dialysis vintage and the higher levels of comorbidity seen in the present study in comparison to these previous studies.

In the intervention group, over the course of the study, there were significant improvements in self perceived levels of function and well being (PCS), resulting in an overall improvement of 9.9 points. There were also significant improvements in three of the individual functional domains (RP, PF, and GH) therefore the changes in these individual domains will have strongly influenced the overall change in the PCS score. Initially, there was an increasing trend in the PCS score noted between recruitment and 3 months for the intervention group which was not observed in the control group. A significant increase in the PCS score was then observed at 6 months, which was not mirrored in the control group. However, the scores for the control group at 3 and 6 months appear to suggest a small amount of variability in

patients' perceptions of physical functioning. This is probably because quality of life is a dynamic construct and as a consequence some variability in an individual's perception of their quality of life is expected (Mittal et al 2001). Beyond 6 months, although the PCS score for the intervention group continued to steadily improve, it was not until 12 months that another significant change occurred. This could again be related to the dynamic construct or it could be due to a lack of sensitivity on the part of the SF36v2 to detect smaller but clinically significant improvements in function.

The increase in PCS seen in the present study, may not only reflect improvements in the patients perceived level of physical functioning, but may also reflect wider improvements in morbidity and mortality. Both De Oreo (1997) and Lowrie et al (2003) have suggested that an increase in PCS score of 1 point results in a 2% reduction in mortality and both Knight et al (2003) and De Oreo (1997) reported that a lower PCS score was an independent predictor of hospitalisation.

The observed changes in the individual physical domains suggest that these may not be influenced by exercise or are not influenced by exercise in the same manner. In the intervention group a significant improvement in the PF domain was observed at 3 months and this was then maintained thereafter. Although the results appeared to demonstrate a clear pattern of worsening PF for the control group, this change was not of a magnitude that was statistically significant. The pattern observed in the control group does, however, provide strength to the argument that the observed changes in PF are as a result of the exercise intervention. The improvement seen suggests that patients feel they are less limited in undertaking daily physical activities.

The role physical (RP) domain results, similar to the PF results, significantly increased at 3 months for the intervention group and were maintained thereafter. Although there was no significant change in the RF domain scores in the control group at 3 and 6 months, the pattern appears to mirror that seen in the intervention group. This could suggest that factors other than changes in function are influencing the observed changes. This is perhaps not unreasonable given that the questions relating to this domain score are more subjective than those of the other domains and suggest that emotional well being could have a greater influence on this domain rather than physical well being. In particular, anxiety trait and depressive symptoms have been suggested to influence responses to certain questions on physical function (Vazquez et al 2005).

Unlike the PF and RP domains, there was no significant change in the GH domain at 3 or 6 months for either the control or the intervention group. While there was some variability in the results at 3 and 6 months observed in the control group their perception of their general health remained unchanged. Conversely, the picture for the intervention group at 3, 6 months and beyond is one that is steadily improving and strengthens the view that the changes are as a result of the intervention. The changes, however, were not statistically significant until 12 months. The apparent delayed influence of the exercise intervention on this domain score could be due to the nature of the questions used to quantify general health such that larger changes, sustained over a longer period are required, before patients perceive their general health to be better or worse.

In contrast to the PF, RP and GH domain, there were no significant changes in the BP domain score over time for either the intervention group or the control group. This would suggest that the exercise intervention did not significantly alter

perceptions of bodily pain. Pain is commonly reported in haemodialysis patients and is most frequently related to musculoskeletal pain (Davison 2003), therefore a non significant change in perceptions of pain could be seen as a positive outcome. This result, coupled with the improvements seen in the other domains, suggests that the intervention is unlikely to cause any negative health effects, which may be particularly important in an ageing dialysis population when quality of life is frequently more important than longevity of life.

In comparing the findings of the present study to those of other studies, few previous intradialytic aerobic exercise studies have examined the possible impact on quality of life. Two previous studies reported no significant changes in either the physical component summary score or the associated PF, RP, BP, and GH domain scores (Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-Van-Vlack 2006). In both of these studies, high functioning groups were recruited. In the first study of 2 months duration (Parsons, Toffelmire and King-VanVlack 2004), given that no changes occurred in the objective measurements of function it is not unexpected that a lack of change in perceived function occurred. In the second study (Parsons, Toffelmire and King-VanVlack 2006) of 5 months duration, despite a small (14%) but significant improvement in distance covered in the 6 minute walk test, there was no improvement in perceived function. This is perhaps more surprising, but the authors questioned whether this was due to pre-existing high levels of self reported function and a ceiling effect of the SF36. A third controlled study of 5 months duration (Painter et al 2002) also recruited patients with higher perceived levels of physical functioning, but this time the intervention resulted in a significant improvement in VO_2 peak and a significant increase in the PF domain.

Other exercise studies in HD patients using combined aerobic and resistance, either intradialytic or interdialytic, have also demonstrated significant improvements in either PCS or the associated domains (Oh-Park 2002, Painter et al 2000, van Vilsteren, de Greef & Huisman 2004, Molsted et al 2004, Cheema et al 2007, Ouzoni et al 2009). In addition, controlled studies suggest that whilst some variability in scores for the non-intervention group is the norm, the scores either remain unchanged (Painter et al 2002, van Vilsteren, de Greef & Huisman 2004, Molsted et al 2004, Ouzoni et al 2009) or show evidence of decline (Painter et al 2000, Cheema et al 2007), which is similar to the findings in the present study.

Although one observational study of HD and PD patients found weak to moderate positive correlations between sit to stand performance and time taken to complete 20 foot walk with the PF domain (Kutner, Zhang and McClellan 2000), no previous exercise studies appear to have examined whether any associations between changes in objective function and perceived function exist. In the present study, no significant associations were found between the changes in PCS, PF, GH, RP scores and any other functional outcome measure. There are a number of possible explanations other than smaller numbers in the present study why this might be. The perception of physical functioning has been reported to not always be in parallel with objective physical functioning (Ware et al 2007). This may again be due to the fact that quality of life is a dynamic construct, but could also be because it is not considered a linear construct (Dymek et al 2002, Schwartz and Rapkin 2004, MacEntee 2007). A lack of association could also be due to a lack of sensitivity on the part of a generic questionnaire to detect small but clinically significant changes in objective functional status (Dymek et al 2002). This therefore suggests that whilst the SF36 provides useful information on a patient's perception of their own physical functioning, it should not be used in isolation to quantify or monitor changes in

function. Nonetheless, it is important to emphasise that the direction of change in perceived levels of functioning is the same as that observed in the objective measures of function.

Interestingly, although no associations were found between TUG, sit to stand, handgrip and any clinical outcome measures, associations with perceived function were evident. Negative associations were found between pre dialysis hsCRP and PCS at 3 months and PF at 3 and 6 months. These associations were only of moderate strength and in view of the lack of a consistent association, imply that while inflammation may have some influence on perceived physical functioning there are stronger influences of unknown origin. It is, however, unclear why such an association should exist between perceived levels of function and not objective measures of function.

In summary, in this older stable HD population the results of the present study suggest that significant improvements in both lower and upper limb function are possible as a consequence of a longer term low to modertate intensity exercise intervention. The results of the present study also suggest that significant improvements in self perceived functional well being are possible. As the majority of the improvements were first seen at 3 months in the low intensity phase of the intervention, it is possible that in a more prevalent HD population higher intensity interventions are unnecessary to derive positive benefits in function and well being.

5.4 EFFECT OF EXERCISE ON PSYCHOSOCIAL QUALITY OF LIFE

In contrast to the findings for the PCS score, at recruitment, both groups reported a mental component score (MCS) that was not significantly different from the general population norm score of 50 (Ware et al 2007). This finding is consistent with other observational studies of HD patients (De Oreo 1997, Diaz-Buxo et al 2000, Kalantar-Zadeh et al 2001, Mittal et al 2001, Dwyer et al 2002, Knight et al 2003, Lowrie et al 2003, Cleary and Drennan 2004, Altintepe et al 2006) and would suggest that HD patients have similar levels of psychosocial well being as the general population. This can perhaps be explained by the suggestion that in chronic disease psychological adaptation occurs, which in turn blunts the impact on perceived psychological well being (Mittal et al 2001). However, in comparison to the three other studies of intradialytic exercise reporting SF36 scores, the results of the present study suggest that the recruited group has lower levels of psychosocial well being (Painter et al 2002, Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-VanVlack 2006). Why this might be is not immediately evident, but could perhaps be explained by the impact of a longer dialysis vintage, higher levels of comorbidity and lower levels of physical functioning on psychological well being.

In comparison to norm based scores for the individual mental health domains, patients in both groups at recruitment were reporting interference of their psychological well being on their normal social activities (SF), that they felt more often tired and worn out (VT) and that they experienced emotional problems with daily activities (RE). In addition, the intervention group, but not the control group felt more nervous and depressed (MH). Although there is a greater variability in the reported results for psychosocial domain scores, in comparison to previous

observational studies of HD patients the recruited population are reporting lower domain scores for SF, RE and MH, but not VT (Khan et al 1995, De Oreo 1997, Merkus et al 1997, Rebello et al 1998, Blake et al 2000, Diaz-Buxo et al 2000, Cleary and Drennan 2004, Altintepe et al 2006, O'Sullivan & McCarthy 2007). The recruited population are also reporting lower domain scores than in comparison to previous intradialytic exercise interventions (Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-VanVlack 2006).

Over the course of the study, as evidenced by a lack of change in the MCS score, between recruitment, 3 and 6 months, neither group reported a significant change in their psychosocial well being. There was also no significant change in MCS observed for the intervention group at 9 and 12 months.This finding is consistent with previous intradialytic aerobic exercise studies and suggests that exercise has little impact on overall psychosocial well being in patients who report good pre-existing levels of psychosocial well being (Painter et al 2002, Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-VanVlack 2006).

However, while there was no significant change in the mental component summary score, significant changes were observed in two of the individual mental health domains, social functioning (SF) and vitality (VT). In the case of the SF domain, in both groups there was no significant change between recruitment, 3 and 6 months, and a significant change did not occur in the intervention group until 12 months. Arguably, as the pattern of change for both groups between recruitment, 3 and 6 months, demonstrates considerable variability, attributing the changes in SF to the exercise intervention is probably misleading. Again no significant changes in VT were seen between recruitment 3 months and 6 months in either group. However in contrast to the results for SF, the pattern of change between recruitment and 6

months demonstrates small but consistent improvements in VT for the intervention group with the control group essentially remaining unchanged. As there is less variability in these results, it is reasonable to assume that the significant change seen at 9 months and maintained at 12 months is secondary to the exercise intervention. The changes in this domain imply that latterly the intervention group perceived themselves to be less tired and fatigued than at recruitment.

In comparison to previous studies of intradialytic aerobic exercise, significant changes in VT and SF domains have not been observed (Painter et al 2002, Parsons, Toffelmire and King-VanVlack 2004, Parsons, Toffelmire and King-VanVlack 2006). However, these studies recruited groups who reported significantly higher pre-existing levels of psychosocial well being at baseline. As a result, it is possible that changes in function could not influence this further. Improvements in VT scores have, however, been observed as a consequence of a 3 month combined resistance and aerobic intradialytic study (van Vilsteren, de Greef & Huisman 2004) and a 3 month intradialytic resistance intervention (Cheema et al 2007). These were both controlled studies and similar to the present study, scores for the control group either remained unchanged (van Vilsteren, de Greef & Huisman 2004) or declined (Cheema et al 2007). These findings would therefore suggest that longer term improvements in the VT domain are feasible in response to an aerobic intervention.

Further to the exploration of associations between the changes in self reported functional well being and other outcome measures, associations between changes in self reported psychosocial well being were also explored. Only one association of fair to moderate strength between perceived levels of vitality and CMC was found. The association would imply that improvements in lower limb FFM positively influenced perceptions of energy levels. This association was observed at 3, 6 and 9

months, but not 12 months. The possible loss of an association at 12 months could be due to reducing patient numbers.

In summary, these findings suggest that while the exercise intervention resulted in positive effects on overall functional well being, it did not result in positive effects on overall psychosocial well being. However, the findings suggest that in the absence of an overall effect on psychosocial well being, that in the longer term positive effects on individual psychosocial domains may be possible.

5.6 EFFECT OF EXERCISE ON NUTRITIONAL STATUS

Another aim of this study was to examine the impact of the exercise intervention on nutritional status. At recruitment, there were no significant differences in BMI between the two groups and based on the BMI at recruitment, both groups would be considered overweight (WHO 1995). This finding is perhaps unexpected given the wide spread assumption that HD patients are undernourished, but is in keeping with other more recent observational and exercise studies in the HD population (Cooper et al 2000, Koufaki, Mercer & Naish 2002, Dumler and Kilates 2003, Donadio et al 2005, Storer et al 2005, Zamojska et al 2006, Cheema et 2007, Toussaint, Polkinghorne & Kerr 2008). This would also suggest that the level of BMI observed in the present study is in keeping with the secular increase in BMI observed in the general population (Corish et al 2000).

Despite recruiting an overweight population, the anthropometric results at recruitment demonstrated that both the control and intervention group had a lower than average FFM in comparison with normative data and that this was more pronounced in the lower limbs. Given the positive correlation between CMC, sit to

stand performance and handgrip strength this finding suggests that a lower FFM could be negatively influencing function. The recruited population in the present study had, in contrast to other HD studies of patients with similar BMI's, a higher upper arm FM and similar or lower upper arm FFM (Marcen et al 1997, Chumlea et al 2003, Kopple et al 2007). Whilst there are fewer studies in the HD population utilising lower limb anthropometry, the recruited population in the present study had similar (Dwyer et al 2005) or lower (Wang et al 2005, Cheema et al 2007) calf circumference (CC) measurements.

Comparison of the whole body composition results in the present study with other studies is complicated by differences in BIA techniques (eg single, dual, multi frequencies); timing of measurements (eg pre or post dialysis), age and BMI. However some general observations can be made. Kyle et al (2001) published percentiles for FFM and FM measured by single frequency in over 5,000 healthy subjects aged 15-98 years. In comparison with this data, it would appear that the recruited group have a FFM comparable to the 25^{th} -50^{th} percentile and a FM comparable to the 75^{th} -90^{th} percentile. These results reinforce the anthropometric findings and suggest that the recruited population in the present study has a higher than average total body FM and lower than average total body FFM.

Comparisons of the whole body composition results in the present study with those in the HD population are again complicated by differences in methodology as outlined above and a lack of normative data for FM and FFM in the HD population. However, in comparison to observational studies of HD patients with similar BMI's, it would appear that at recruitment the patients in the present study have higher (Chertow et al 1995, Dumler & Kilates 2003) or similar (Donadio et al 2005) levels of FM and similar (Donadio et al 2005) or lower levels of FFM (Chertow et al 1995,

Dumler & Kilates 2003). In addition, one previous intradialytic aerobic study has reported information on whole body composition (Macdonald et al 2005) as have two other interdialytic HD exercise studies (Kopple et al 2007, van den Ham et al 2007). The recuited populations in all of these previous studies were approximately 10 years younger, had a shorter dialysis vintage, lower BMI's, higher levels of FFM and lower levels of FM in comparison to those recruited to the present study. It could therefore be surmised that the body composition observed in the present population is negatively influencing levels of function.

Over the course of the present study, there were no significant changes in either weight or BMI in either group at 6 months. Beyond 6 months there was also no significant change in BMI for the intervention group. This finding is consistent with the few intradialytic aerobic studies who have reported weight changes or changes in BMI (Frey, Mir & Lucas 1999, Koufaki, Mercer & Naish 2002, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005). Despite no significant changes in weight or BMI there were small but significant changes in upper and lower limb anthropometry that were outwith the technical error of measurement of the author, suggesting that changes in regional body composition were occurring. Both the mid arm muscle circumference (MAMC) and calf muscle circumference (CMC) increased significantly over 12 months by 8% and 5% respectively, suggestive of an increase in both upper and lower skeletal FFM. Significant changes in MAMC were first seen at 6 months in the intervention group, in contrast to an unchanged MAMC for the control group. While beyond 6 months subsequent increases in MAMC were also seen, these were not statistically significant. In comparison to MAMC an earlier change in CMC was noted at 3 months with a subsequent maintenance of this change until 12 months when another significant increase was seen. It is postulated that the earlier change in CMC in comparison to MAMC is related to the form of exercise being used.

Although there was no significant change in CMC for the control group, the pattern for CMC appears to suggest an increase in CMC as well. However, this can be explained by two patients in this group who had visual signs of lower leg oedema at 3 and 6 months.

The significant increases in CMC and MAMC in the intervention group were accompanied by a significant decrease in calf skinfold at 9 and 12 months and a trend towards a decrease in TSF. Neither of these changes was observed in the control group. These findings would suggest that skeletal FM was decreasing as FFM was increasing.

Whilst none of the previous intradialytic aerobic exercise studies examined changes in anthropometric measurements, other short term exercise studies conducted in HD populations have and have reported changes. Headley et al (2002) after a 12 week interdialytic resistance intervention observed a significant increase in percentage FM derived from seven skinfolds. However, the authors questioned the reliability of their measurements and the possibility that changes in ECW had affected the skinfold compressibility. Kopple et al (2007) after 3 months of different interdialytic interventions observed combined significant decreases in skeletal FM and increases in FFM. Cheema et al (2007) in their study of 3 months resistance exercise observed significant increases in mid arm circumference and mid thigh circumference. It is, therefore, reasonable to conclude that changes can occur at 3 months and that further changes beyond 3 months are also possible as demonstrated in the present study.

The increase in skeletal FFM is perhaps surprising given that the intervention was primarily an aerobic intervention. Nevertheless increases in muscle size have been

seen in a small study of older healthy women after a 3 month low to moderate aerobic cycling intervention (Harber et al 2009). It is postulated that the increases in FFM are as a result of alterations in protein synthesis and/or proteolysis with a resulting shift towards a positive protein balance. Increases in muscle IGF-1, mRNA expression, insulin sensitivity, along with decreases in muscle cytokines, metabolic acidosis and blunting of dialysis related proteolysis are all possibilities (Siew et al 2007, Mitch & Price 2003, Pupim, Flakoll & Ikilzer 2004, Biolo et al 2005, Kopple et al 2007, Muscaritoli et al 2009). It has also been shown in healthy individuals that the consumption of protein and carbohydrate 1-3 hours after resistance exercise augments protein synthesis (Phillips 2004). Therefore, it is possible that while dietary intake did not increase, there is a greater sensitivity to nutrients consumed in the post exercise period (Pupim et al 2004b). Furthermore, it is surmised that the observed reduction in skeletal FM is as a consequence of increases in fatty acid oxidation, known to occur as a result of aerobic exercise training and to progressively increase during prolonged (30 minutes or more) low to moderate intensity exercise (Horowitz 2003). It is also evident that the majority of plasma fatty acids available to skeletal muscle during exercise are derived from subcutaneous FM making this a plausible explanation for the changes seen (Horowitz 2003).

In contrast to the regional changes observed, there were no significant changes in whole body composition measured using DFBIA. Similar results have been observed in other shorter studies of intradialytic aerobic exercise (Macdonald et al 2005), intradialytic resistance exercise (Kopple et al 2007) and interdialytic combined aerobic and resistance exercise (van den Ham et al 2007). This appears to contradict the anthropometric findings, but it is possible that the magnitude of the change seen in skeletal FM and FFM has not been sufficient to be detected by BIA. This would, therefore, support the use of anthropometry to better understand the

impact of exercise interventions on body composition. Overall given that there is some evidence to suggest that over time FM increases and FFM decreases in HD patients (Ishimura et al 2001), a non significant change in whole body composition could be considered a positive finding and one that will be of benefit in preventing deteriorations in functional status.

Few associations were found between the changes in nutritional status and other outcome measures. The associations between CMC and function have already been discussed and the only other association was between the changes in CMC and changes in haemoglobin. This was a positive relationship found at all time points and strengthened across the course of the study. Such an association has been found between calf muscle and haemoglobin in a large observational study of older healthy individuals (Cesari et al 2004). Whilst the association does not directly attribute cause and effect, it is possible that higher levels of haemoglobin reflect lower levels of cytokine activity which in turn are positively influencing FFM (Cesari et al 2004).

In addition to exploring the influence of exercise on body composition, the possible influence of exercise on appetite and dietary intake was also explored having been neglected in previous intradialytic aerobic interventions. At recruitment, the intervention group perceived their appetite as good and the control group perceived their appetite to be fair/poor (Zabel et al 2009a). Over the course of the study, there were no significant changes in appetite observed in either the intervention or the control group. A likely explanation for a lack of improvement in appetite could be that the accompanying small rise in energy expenditure as a result of the exercise intervention has been insufficient to stimulate the intervention groups pre-existing good levels of appetite further (Bilski et al 2009). However, as hsCRP did not alter

significantly over the course of the study, ongoing systemic inflammation could also be preventing improvements in appetite and therefore intake (Kalantar-Zadeh et al 2004). The appetite results also suggest that the levels of exercise intensity used in the present study did not cause a transient inhibition of appetite (Blundell and King 2000). This finding may be equally important given the propensity for HD patients and in particular older HD patients to experience poor levels of appetite, reported to worsen on dialysis days and to be negatively associated with outcome (Wright et al 2001, Burrowes et al 2002).

In healthy subjects with normal appetites, the overall evidence points to a weak coupling of energy intake and energy expenditure induced by physical activity (Blundell & King 2000). This is primarily thought to be due to stronger behavioural influences on appetite such as habitual patterns, olfactory influences (Yeomans 2006), mood and social isolation (Blundell and King 2000) and also appears to be evident in the present study. Additional considerations in this population could also be the influence of long standing dietary restrictions and side effects of medications. As no other exercise studies in HD patients have examined appetite it is not possible to comment on these findings in the wider context.

It is difficult to be conclusive about changes in dietary intakes due to the small number of individuals who returned food diaries. At recruitment the intervention group were not meeting the recommended intakes for energy and protein (Fouque et al 2007). However, given that the group is an overweight stable population, it is possible that despite the steps taken to ensure accuracy, intakes have been underreported (Kloppenburg, de Jong & Huisman 2002). A finding observed more frequently in individuals with higher BMI's (Fouque et al 2007). It is also possible that the current recommendations over estimate energy expenditure given the

increasing age and low levels of physical activity observed in the prevalent HD population (Fouque et al 2007). Most studies including a large American study (Dwyer et al 2002 and 2005) report intakes in the region of 20-25kcal/kg/day and 0.9-1.0g/kg/day protein and these are similar to the findings in the present study. Over the course of the present study, there was no significant change in energy, protein, and fat or carbohydrate intakes in either group. Furthermore, there was also no significant change in PCR observed in either group. However it should be noted that in anabolic conditions such those potentially observed in the present study, PCR can underestimate actual dietary protein intakes. None the less, the findings of both the diet diaries and PCR mirror other HD exercise studies of shorter (Frey, Mir & Lucas 1999, Cheema et al 2007, Kopple et al 2007) or identical time scales (Cappy, Jablonka, Schroeder 1999). This would suggest that exercise as an intervention is unlikely to significantly alter dietary intakes.

Studies in healthy individuals suggest that exercise may modify macronutrient preferences and food choices with a preference for high fat foods (Blundell and King 2000, Bilski et al 2009). Based on the analysis of the macronutrient intakes, this does not appear to be the case in the present study. Arguably, this is a positive finding given the higher cardiovascular mortality risk in the HD population and something to be avoided despite the increase in fatty acid utilisation in muscles during exercise.

In summary, this longer term low to moderate intensity aerobic intervention resulted in positive improvements in skeletal FM and FFM. However, these were not of significant magnitude to influence changes in whole body composition. It can also be tentatively concluded that such an intervention is unlikely to acutely impact on dietary intakes in well nourished patients with good pre-existing levels of appetites.

This may not, however, be the case in undernourished patients or those with poor pre-existing appetites and these are areas that warrant further exploration.

5.7 EFFECT OF EXERCISE ON CLINICAL STATUS

In addition to examining the effects of the exercise intervention on function, quality of life and nutritional status, the study also aimed to explore the effects of the exercise intervention on clinical status.

At recruitment, there were no significant differences between the intervention group and control group in any of the clinical parameters examined. Over the course of the study, beneficial effects on clinical status were observed in the intervention group. These included a significant increase in effective blood flow rates at 9 and 12 months, despite no change in prescribed blood flow rates. Whilst the changes in effective blood flow rates occurred after the loss of the control group, the pattern in the control group up to 6 months suggests a stable, rather than a fluctuating or changing, picture. It is, therefore, plausible that the improvements in effective mean blood flow are as a result of the exercise intervention and longer term changes such as improvements in peripheral vascular resistance could explain this (Painter 2005).

Further to the significant increase in effective blood flow rates, a significant decrease in post dialysis serum urea levels also occurred in the intervention group at 9 and 12 months. As the change in post dialysis serum urea coincided with the changes in effective blood flow rates, the changes are considered to be related. Although the results for post dialysis serum urea up to 6 months suggest a similar pattern between the intervention and control group, it should be noted that the pre dialysis urea in the control group shows a statistically significant trend towards reduction

which is not observed in the intervention group. This in the presence of a constant level of dialysis efficiency would result in lower post dialysis serum urea results. However, despite the increase in effective blood flow rates and decrease in post dialysis serum urea levels, these changes were not of sufficient magnitude to significantly improve dialysis efficiency measured using URR or eKt/v.

Although there was no significant change in eKt/v for either the intervention or the control group over time, there was a trend for an improvement in URR in the intervention group which was not observed in the control group. There were no changes in the prescribed duration, dialysate flow, dialyser type/size or residual renal function that could explain this trend. It is possible that larger study numbers would have resulted in significant changes particularly for URR, but it is also possible that the use of eKt/v in intradialytic exercise studies is not appropriate. eKt/v corrects for post dialysis urea rebound and as exercise is reported to reduce urea rebound (Kong et al 1999) this may invalidate the use of such an equation. In addition although increases in blood flow will influence K, increases in FFM (as demonstrated by MAMC, CMC) will influence V (National Kidney Foundation 2006) which in turn could result in no net change.

Only two previous exercise studies have shown improvements in dialysis adequacy. One was an intradialytic aerobic exercise study of 5 months duration (Parsons, Toffelmire and King-VanVlack 2006) and the other was a 12 month study of combined aerobic and resistance exercise immediately before dialysis (Cappy, Jablonka & Schroeder 1999). Both of these studies had no control group and they used spKt/v rather than eKt/v. In addition, they did not appear to control for other influences such as increases in dialysis time or changes in dialyser size. Consequently further work is required to confirm whether intradialytic aerobic

exercise can improve long term dialysis efficiency and whether this in turn contributes to changes in function.

In addition to the above trend in URR, trends were also seen in the intervention group for lower pre dialysis levels of serum potassium and higher levels of serum bicarbonate. As such, it is likely that these changes are related to the trends towards improvements in dialysis efficiency. However, if the exercise intervention has improved insulin sensitivity (Goldberg et al 1986), it is possible that changes in pre dialysis potassium also reflect an increase in the cellular uptake of potassium (Ahmed and Weisburg 2001).

Although a small one week study of 30-60 minutes of intradialytic aerobic exercise (Vaithilingham et al 2004) suggested that improvements in phosphate removal and potentially serum phosphate levels were possible, no significant changes in serum phosphate or dose of phosphate binders were observed in the present study. Whilst it is possible that a larger sample size may have produced a significant result, it is also possible that exercise sessions of longer than 30 minutes are required to significantly improve serum phosphate levels given the relative size of the intracellular pool of phosphate (Vaithilingham et al 2004). It is, however, worth highlighting that although no significant changes in serum phosphate occurred, at the end of the study the intervention group were meeting the therapeutic target for pre dialysis phosphate levels. This had not been the case at recruitment.

Further to examining the effects of exercise on the above clinical parameters, the possible effects of exercise on hsCRP and leptin were also examined. At recruitment the results for high sensitivity C-reactive protein (hsCRP) demonstrated evidence of low grade inflammation in both groups, consistent with other

observational or intervention studies of HD patients (Hung et al 2002, Johansen et al 2003b, Kopple et al 2007, Toussaint, Polkinghorne & Kerr 2008).

Over the course of the study, whilst decreases in pre and post hsCRP levels were apparent in the intervention group, these were not of a statistically significant magnitude. Conversely, whilst an increase in pre dialysis hsCRP occurred in the control group this was also not statistically significant. These findings would suggest that the exercise programme has not significantly impacted on inflammation. However, as highlighted previously, serum cytokines do not always accurately reflect changes in the local expression of inflammatory markers in muscle (Sapte & Schulze 2004). Additionally, it is possible that a non-significant change in hsCRP is related to the small sample size.

Few HD exercise studies have examined the effect of exercise on proinflammatory cytokines. One previous controlled 3 month intradialytic aerobic study (Toussaint, Polkinghorne & Kerr 2008) demonstrated no significant change in CRP, as did a 5 month interdialytic study (Kopple et al 2007) which utilised combined aerobic and resistance interventions. In contrast to these studies, one controlled 3 month intradialytic study of resistance exercise (Cheema et al 2007) did report a significant decrease in CRP. Additionally, one other uncontrolled 3 month intradialytic resistance intervention reported a decrease in CRP, but it was unclear whether this was significant (Nindl et al 2004). Therefore, the current evidence is equivocal and further work is required to determine whether exercise alone can positively influence circulating levels of hsCRP in HD patients.

Unfortunately, due to the loss of a significant number of leptin samples for patients in both groups at all time points little can be concluded from this aspect of the study.

What can be concluded is that hyperleptinaemia is evident in the recruited population as has been demonstrated in other studies of the HD population (Johansen, Mulligan & Schambelan 1998, Nishikawa et al 1999, Norton 2002, Bossola et al 2004, Wright et al 2004, Mak et al 2006). Whether serum leptin influences appetite, dietary intakes and inflammation or whether serum leptin can be modified by intradialytic aerobic exercise remains unanswered.

As a small number of previous studies had suggested the possibility that haemoglobin (Goldberg et al 1983, Goldberg et al 1986, Miller et al 2002) and perhaps doses of ESAs (Miller et al 2002, Anderson et al 2004) could be influenced by exercise these parameters were also examined in the present study. At recruitment both the intervention group and the control group were meeting the therapeutic target for haemoglobin and haematocrit and there was no significant difference between the groups. There was also no significant difference in the ESA/Hct index between the two groups.

Between 0 and 6 months a progressive and significant decline in haemoglobin was observed in the control group. In contrast a progressive and significant increase was observed in the intervention group. Simultaneously, there was a progressive, albeit non-significant, increase in haematocrit observed in the intervention group, which was not seen in the control group. Although changes in TBW could cause increases or decreases in these particular parameters, there were no significant changes in TBW observed in either group.

ESAs are being constantly titrated to achieve a therapeutic target for haemoglobin and haematocrit of 11-12g/dl and >33% respectively (Singh 2008). Therefore, in response to a significant increase in haemoglobin or haematocrit the dose of ESA

will be reduced and in response to a decrease in haemoglobin or haematocrit the ESA dose will be increased. As such, these changes are reflected in a significant reduction in the ESA/Hct index from 6 months onwards in the intervention group with a reverse pattern of change in the control group. As the ESA/Hct index is considered to reflect responsiveness to ESA (Gunnell et al 1999, Kalantar-Zadeh et al 2003), it is postulated that the changes in haemoglobin seen in both groups at 6 months are as a consequence of changes in responsiveness to ESA.

Responsiveness to ESA can be affected by iron deficiency, inflammation, inadequate dialysis and hyperparathyroidism, use of ACE inhibitors, malignancy and nutrient deficiencies (Barany et al 1997, Albitar et al 1998, Kalantar-Zadeh et al 2003, Del Vecchio et al 2005, Priyadarshi and Shapiro 2006, Locatelli et al 2006, Johnson, Pollock, Macdougall 2007, Bradbury et al 2009). As malignancy was a criteria for exclusion and none of the patients received IV iron beyond the standard maintenance dose over the course of the study or had a parathyroidectomy, changes in levels of inflammation, dialysis efficiency and ACE inhibitors are considered to be the most likely explanations for the observed changes.

Inflammation is thought to directly inhibit erthyropoiesis and promote apoptosis of erthyroid precursors (Johnson, Pollock and Macdougall 2007). Although there was no significant change in serum hsCRP levels in the intervention group, it has already been stated that serum hsCRP may not be accurately reflecting changes in muscle cytokines. Therefore, changes in muscle cytokines could be one mechanism that explains the observed changes. Although the mechanism is unclear, improvements in dialysis efficiency are also thought to improve responsiveness to ESA, by decreasing circulating levels of substances known to inhibit erythropoiesis (Macdougall 2001). As there was a trend to an improvement in URR and a

significant decrease in post serum urea levels, this is another possibility. Furthermore, whilst more controversial, the use of ACE inhibitors may also cause hyporesponsiveness to ESA by increasing circulating plasma levels of *N*-acetyl-seryl-aspartyl-lysyl-proline which have been shown to inhibit erythropoiesis (Albitar 1998, Macdougall 2001, Priyadarshi and Shapiro 2006, Johnson, Pollock, Macdougall 2007). As such, decreases in ACE inhibitor doses, seen in the present study, albeit non-significant, pose another contributory mechanism for improvements in responsiveness to ESA. Recently acidosis and hyperphosphataemia have also been associated with an increased requirement of ESA (Diskin et al 2006). The suggested mechanism is that the presence of acidosis and hyperphosphataemia results in a rightward shift in the oxygen-haemoglobin dissociation curve resulting in a down regulation of erythrocyte receptors (Diskin et al 2006). As both improvements in serum bicarbonate and phosphate levels were observed, although non-significant, it is possible that this is another mechanism by which improvements in responsiveness to ESA are occurring.

In comparison to the results seen in the present study for haemoglobin and changes in ESA, four previous intradialytic aerobic studies of 5 months duration or less observed no significant changes in haemoglobin levels. They, however, neglected to control for changes in ESA doses or possible factors influencing responsiveness to ESA (Moug et al 2003, Parsons, Toffelmire & King-VanVlack 2004, Parsons, Toffelmire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008). However two intradialytic aerobic exercise studies of 6 months duration, which used similar exercise protocols to the present study, did observe changes. Miller et al (2002) observed a significant increase in haematocrit and a significant decrease in ESA dose and Anderson, Boivin & Hatchett (2004) observed an increase in haematocrit and a trend towards a decreasing ESA dose. Furthermore, one 12 month study of

interdialytic exercise conducted in the pre ESA era also reported significant improvements in haemoglobin and haematocrit levels unrelated to changes in plasma cell volume (Goldberg et al 1986). Unfortunately, in none of these studies were changes in inflammation or other known influences measured or reported and none explored possible mechanisms.

A reduction in ESA dose, as demonstrated in the present study, has the potential to significantly decrease the costs associated with anaemia management. More importantly, evidence from large studies suggests that higher ESA doses are associated with toxicity and an increased mortality (Zhang et al 2004, Drueke et al 2006, Sing et al 2006) therefore the possibility that exercise can decrease the requirement for ESA's warrants further investigation.

As a small number of previous intradialytic aerobic exercise studies (Painter et al 1986, Anderson et al 2004, Macdonald et al 2005) had suggested that exercise could improve blood pressure and decrease the need for antihypertensives, this was the final facet of clinical status to be explored. At recruitment, there were no significant differences in systolic or diastolic blood pressure between the groups. Whilst no significant improvements in systolic blood pressure (SBP) were observed in either group at 3 months, a significant decrease in SBP was observed in the intervention group at 6 months which was not seen in the control group. This reduction was maintained in the intervention group at 9 months, but appears to return towards baseline at 12 months. The reason for this apparent return to baseline is unclear. No significant changes in interdialytic weight gains, TBW, ECW volume which have been suggested to influence blood pressure were observed (Lopez-Gomez et al 2005, Charra 2007). However, as blood pressure is being constantly titrated against a therapeutic target, it is possible that in response to a

continual pattern of falling levels, further reductions in antihypertensive medications between 9 and 12 months resulted in a return towards baseline.

Improvements in blood pressure as a consequence of exercise are thought to occur due to changes in plasma volume and/or peripheral vascular resistance (Painter et al 1986, Kouidi 2001, Mustata et al 2004). In the present study the results suggest that decreases in peripheral vascular resistance are most likely, but it is also possible that the observed reduction in ESA dose in the present study could be contributing (Kanbay et al 2007).

Three previous intradialytic aerobic interventions (Painter et al 1986, Anderson, Boivin & Hatchett 2004, Macdonald et al 2005) reported significant reductions in systolic blood pressure. Two of these studies were of 6 months duration (Painter et al 1986, Anderson, Boivin & Hatchett 2004) and one study was of 3 months duration (Macdonald et al 2005). In addition, whilst all three of these studies reported reductions in antihypertensive medications, only one saw a significant reduction (Macdonald et al 2005).

In summary, significant increases were observed in effective blood rates along with a significant reduction in post dialysis urea, ESA/Hct index, haemoglobin, ESA dose and systolic blood pressure. These significant changes coupled with trends towards a decrease in total antihypertensive dose, pre dialysis potassium, increased URR and pre dialysis bicarbonate; suggest that a low to moderate intensity programme such as this could positively impact on multiple aspects of clinical status.

5.8 STUDY LIMITATIONS AND FUTURE RESEARCH

A lack of a power analysis and the apparent small sample size in the present study ultimately raises concerns over the type I and type II error rate and therefore the strength of the findings. However, a retrospective power analysis based on the effect size of the functional outcome measures (Sit to Stand, Timed Up and Go, Handgrip) demonstrated that to achieve 90% power with a type I error rate of p=0.01 a sample size of 6-9 subjects was required. Furthermore, it should also be recognised that the numbers in the present study are comparable to or greater than those of previous intradialytic aerobic studies (Frey, Mir & Lucas 1999, Painter et al 2002, Moug et al 2003, Anderson, Boivin & Hatchett 2004, Parsons, Toffelmire & King-VanVlack 2004, Macdonald et al 2005, Parsons, Toffelmire & King-VanVlack 2006, Toussaint, Polkinghorne & Kerr 2008).

The use of a non- randomised controlled study could also be considered a limitation. However based on what was already known about the benefits of exercise in HD patients and in keeping with the views of a number of authors in the field (Painter 2000, Miller et al 2002), it was considered inappropriate to use a RCT design whereby patients who wished to exercise may be excluded for a prolonged period of time. A cross over design was possible, but deemed impractical due to the length of the intervention and the difficulties associated with the interpretation of data caused by a loss of the benefits in the group randomised to exercise first (Shephard 2002). Therefore, control was achieved by patients acting as their own controls (-1 month), and the recruitment of a non-randomised contemporaneous control group. It is also recognised that the loss of the contemporaneous control group at 6 months poses a further limitation to the findings of the present study. Despite this it is recognised that an RCT remains the gold standard in confirming or refuting the effects of such

interventions, and as such it can be argued that the findings of the present study are therefore preliminary and that an RCT should be the next step. Furthermore, such an RCT could be appropriately powered by selected data from the present study.

It is also acknowledged that as a consequence of the proxy measure used to regulate and progress exercise intensity (eg RPE), coupled with a lack of measured work rates, that it is not possible to specifically quantify the level of work that elicited the observed changes in the present study. Furthermore, it is also recognised that the present study has provided no direct evidence to suggest improvements in aerobic capacity have occurred. Therefore, it is accepted that the observed changes may have occurred without any significant improvement in aerobic capacity (Painter 2005). However, despite these limitations, improvements in function, quality of life, nutritional and clinical status were observed in the intervention group and were not seen in the contemporaneous control group. Whilst it could be argued that another limitation of this study is that it involved one single centre only, it is considered that as the population recruited in the present study were more representative of the current prevalent HD population that the findings are likely to be applicable to the wider HD community.

The results of the present study have also highlighted areas that could provide the focus for future work. These include further work to extend and confirm the reliability of DFBIA in the long term monitoring of body composition at an individual level, particularly in an overweight HD populations. Further exploration of the impact of such an exercise intervention on insulin sensitivity and arterial compliance would be of relevance and may help to expain the observed changes in HGS. In addition the impact of exercise on responsiveness to ESAs would be another area for further exploration.Finally, as there is some evidence from studies of healthy older

populations suggesting that hyperparathyroidism and low vitamin D status negatively affects function, the exploration of these as confounding variables In the HD population would be warranted (Visser, Deeg & Lips 2003, Bischoff et al 2004).

CHAPTER 6: SUMMARY AND CONCLUSION

The results of this study suggest that a long term low to moderate exercise intervention in a group of dialysis patients with a co-morbidity profile representative of the prevalent dialysis population could produce significant functional benefits. Many of the observed improvements were similar to those found in previous studies of younger, healthier HD patients utilising higher intensity interventions. These improvements occurred in this progressive exercise intervention despite relatively little individual supervision and without individual exercise prescriptions. Such improvements in function were not evident in the contemporaneous control group. Several associations were also found between function and nutritional and clinical outcome measures.

The observed functional improvements are likely to have wider implications by positively influencing activities of daily living and cardiovascular health in this functionally impaired clinical population. Future projections for the Scottish dialysis population are such that the numbers of patients requiring HD as part of RRT will increase exponentially. It is likely therefore that an intervention that can be facilitated primarily by dialysis unit staff may potentially provide significant cost savings for the NHS; particularly in terms of improving cardiovascular health and reducing the risk of cardiovascular related events which are prevalent in this population. Although the results suggest that the exercise intervention has the potential to be easily incorporated into the routine care of HD patients, as the onus is on dialysis staff, further work may be required to minimise barriers to the implementation of such an exercise programme, in order to optimise and maintain patient participation.

In the present study, improvements were also seen in perceived functional well being and aspects of psychosocial well being. Such improvements in well being were not evident in the contemporaneous control group. It can be argued that this finding is equally important given that an ageing dialysis population is likely to rate quality of life more highly than longevity of life.

In addition, this longer term exercise intervention would appear to have the potential to produce several favourable changes in clinical status such as improved blood pressure, effective dialysis blood flow, reduced post dialysis serum urea and a reduced need for ESAs. However unlike previous exercise studies the intervention did not produce any significant improvements in dialysis adequacy, systemic inflammatory markers or reductions in antihypertensive medications. In addition it did not significantly impact on appetite or dietary intake and was unable to provide any further insight into the role of leptin. Furthermore, while at a whole body level the intervention served to maintain nutritional status, the results suggest that such an exercise intervention could result in small but significant and favourable changes in skeletal FFM which in turn are likely to positively influence functional status.

The assessment of nutritional status in HD patients is notoriously difficult because of changes in TBW, however the validation of the DFBIA and anthropometric measurements suggest that at a population level DFBIA is suitable for assessing total FM and FFM. However following Bland-Altman analysis it is evident that at higher BMI's the current prediction equations will over estimate FM and underestimate FFM. These results also suggest that DFBIA is not sensitive to small, but significant changes in regional FM and FFM as seen in the exercise intervention study. This would therefore support the use of anthropometric measurements such as circumferences and skinfolds. In particular greater consideration should be given

to the use of calf circumference and calf muscle circumference. These measurements were found to not only correlate more highly with total FFM, but were also found to be associated with functional status along with aspects of quality of life and clinical status.

In conclusion this study has shown that a progressive longer term low to moderate intensity exercise intervention could provide functional, clinical and nutritional benefits along with improvements in quality of life. Consideration should therefore be given to the potential of such an exercise intervention being incorporated into the routine care of HD patients, which in turn could provide multiple benefits and potential cost savings in an ever increasing and ageing dialysis population.

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